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Lung

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Triggering of the systemic inflammatory response syndrome (SIRS) by conditions such as sepsis, multisystem trauma, shock (and massive transfusions), burns, and pancreatitis produces a pulmonary vascular flood of products of the activated humoral cascade system, where inflammatory cells, bacterial toxins, and toxin-produced cellular mediators clearly assume responsibility. Depending on its severity this diffuse injury is characterized as acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). ALI is a syndrome of inflammation and increased permeability that leads to physiologic, radiologic, and clinical abnormalities. When ALI is severe, ARDS is the term used to describe the condition. The consensus definition of ALI includes (1) acute onset; (2) $PaO_2/FiO_2 \leq 300$; (3) bilateral infiltrates on frontal chest radiograph; and (4) pulmonary artery wedge pressure $\leq$ 18 mmHg, or in the absence of a pulmonary artery catheter no clinical evidence of left atrial hypertension.[1] The consensus definition of ARDS is ALI with $PaO_2/FiO_2 \leq 200$. Although ARDS can be primary (due to direct causes such as pneumonia and gas inhalation), it is more strongly linked to outside lung events, which appear to trigger the systemic inflammatory syndrome (SIRS). This type of ARDS is called secondary (or indirect) and is often associated with the multiple organ dysfunction syndrome (MODS).

Acute Respiratory Distress Syndrome

Etiology and Association with MODS

Garber et al. in 1996 reported a meta-analysis of 83 studies related to risk factors for ARDS.[2] The strongest evidence for cause and effect in this study was demonstrated by SIRS associated with sepsis. Of the other four links to cause and effect (aspiration, multisystem trauma, multiple transfusions, and disseminated intravascular coagulation) three of the four were likely SIRS-related as well.

Sepsis represents the most common cause of SIRS-induced ARDS. Sepsis-induced ARDS usually occurs in the context of MODS. Bell et al. demonstrated nonpulmonary organ failure in 85% of patients with ARDS and noted a significant relation between the development of organ dysfunction and infection.[3] Knaus et al. found that 76% of ARDS patients (with sepsis as the most frequent cause) exhibited nonpulmonary organ dysfunction.[4] Shock, metabolic acidosis, and altered mentation were the most common organ dysfunctions. Nonsurvivors had a significantly larger number of organ dysfunctions. Herbert et al. reported a series of 154 consecutive septic patients and demonstrated that ALI and ARDS were the most common forms of organ dysfunction (74 patients).[5] In this study pulmonary dysfunction correlated poorly with the likelihood of death. Estimation of the incidence of SIRS-induced ARDS is difficult because authors have used different clinical criteria for its definition. The ability to define incidence and outcome more precisely, however, has been significantly improved by consensus definitions of ALI and ARDS. The incidence of ARDS is likely to be 3/100,000 to 74/100,000 population.[6]

Pathophysiology

The SIRS-associated inflammatory response manifested in the lung involves a multitude of humoral mediator systems, inflammatory cells, and bacterial toxins.[6] Neutrophilic infiltrates predominate in histologic samples from the lungs of patients with ARDS. Bronchoalveolar lavage (BAL) demonstrates high neutrophil counts and high concentrations of neutrophil degranulation products. Neutrophil-associated oxidant activity increases. Oxidant injury is likely an important component of SIRS-related lung injury. This has been demonstrated in animal models following gut ischemia/reperfusion. Defective surfactant activity may result through oxidant attack on lipid or lipoprotein components, inhibition by plasma-derived proteins that gain access to the alveolar space, or direct type 2 pneumocyte injury.

The complex interaction between endothelial cells and neutrophils leads to endothelial cell damage with formation of pulmonary edema and production of vasomotor disturbances of the pulmonary circulation. Toxin-induced formation of tumor necrosis factor (TNF) and interleukin-8 (IL-8) by macrophages is important in this response. The primary function of IL-8 is neutrophil activation and chemotaxis. TNF promotes neutrophil adherence to the endothelium and pulmonary circulatory vasoconstriction. Lipid mediators such as platelet-activating

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factor, leukotrienes, and prostanoids are also important in augmenting inflammation and producing vascular reactivity.

There is much current interest in the role of coagulation cascade activation in the production of ARDS in patients with SIRS. Activation of the coagulation system by TNF, IL-1, and plasminogen activator inhibitor may be important in the development of ARDS. In the injured alveolar compartment, fibrin deposition is initiated by increased activity of the intrinsic coagulation pathway (tissue factor associated with factor VII) and the contact coagulation pathways is also activated. Local fibrinolysis is generally impaired.

The perpetuating inflammation at the gas-exchange level is responsible for lung pathophysiology, which is characterized by interstitial and alveolar edema, hyaline membrane formation, atelectasis, gas-exchange abnormalities, increased pulmonary vascular resistance, and microthrombi. Clinical changes include hypoxemia, increased deadspace, and markedly reduced lung compliance.

Various patterns of organ dysfunction may occur with SIRS-induced lung injury. In some patients early onset of interstitial and alveolar edema predominate, whereas in others serious gas-exchange disturbances characterized by ventilation–perfusion mismatch may be accompanied by only moderate edema formation, seen on radiologic examination.

Neutrophil recruitment to the lung is accomplished through vascular adhesion molecules, which are upregulated in SIRS. There is direct linkage between cytokines such as TNF and IL-1 and expression of vascular adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1). Complement activation also has diverse effects on the expression of endothelial adhesion molecules. Endothelial changes in SIRS-induced ARDS contribute to regional increases in vascular resistance and hypoperfusion. Multiple inflammatory stimuli synergistically promote neutrophil-mediated tissue injury through priming and activation. Platelet-activating factor is important in this priming process. The lung has the ability to autoregulate, and the importance of antiinflammatory cytokines such as IL-10 in containment of the inflammatory response is now recognized.

Nonsepsis SIRS-Induced ARDS

The adverse effects of hypothermia, hypotension, shock, and multiple transfusions on coagulation are well documented. After major trauma, hemorrhagic shock, or surgical procedures characterized by major blood loss, the concentrations of TNF, IL-1, and IL-6 are increased. High concentrations found during the early postinjury period are associated with increased risk of ARDS development and mortality. In addition, in patients with accidental trauma severe injury produces rapid, large increases in circulating concentrations of cytokines that may contribute to the development of ARDS. An increase in the level of urinary leukotriene E_4 has been demonstrated in burn patients with severe injuries and SIRS who develop ARDS.

Most patients undergoing cardiopulmonary bypass (CPB) recover uneventfully. However, in a small percentage of these patients ARDS complicates the postoperative period; and when it occurs it may be profound. Mortality is high when MODS develops in these patients. The cause and pathophysiology of post-CPB complications are not clear. Sinclair and colleagues calculated the protein accumulation index (PAI) as a BAL marker of integrity of the alveolar capillary membrane following CPB.[7] Changes in the integrity of the gut barrier membrane was also documented in this study. An elevated PAI was found to correlate with both longer operative bypass time and the postoperative serum myeloperoxidase level. This study confirmed that significant microvascular injury complicates CPB even in the absence of significant clinical sequelae, as only 1 of the 20 patients developed ARDS.

Acute respiratory distress syndrome may be seen during pregnancy and is associated with maternal mortality similar to that of nonpregnant patients. The main risks for development of ARDS are hemorrhage, infection, and toxemia. When maternal deaths occur, they are typically in the setting of ARDS plus other organ dysfunctions (MODS).

Predictors of Development

There is an association between massive transfusion and ARDS. That transfused blood is foreign protein and that it is often passed through sophisticated machines and devices, such as during CPB and autotransfusion, may also be important. We should be reminded of the statement by Lister in 1863: "I have only lately been aware of the great influence exerted upon the blood by exposure for a very short time to a foreign solid, and I feel that many of my own experiments, and many performed by others, have been vitiated for want of this knowledge."

Acute respiratory distress syndrome is seen in a significant percentage of patients during the early post-bone marrow transplant (engraftment) period. It is a major cause of morbidity and mortality. This type of ARDS has been linked to a generalized capillary leak syndrome. Some have suggested that the endothelial damage may be related to graft-versus-host disease (GVHD), whereas others have demonstrated release of TNF and IL-2 unrelated to GVHD preceding development of this injury.

General Studies

Bone and colleagues studied the serial development of organ dysfunction in patients admitted to an intensive care unit (ICU).[8] They noted that lung dysfunction dominated the early clinical course. When respiratory function was supported, other organ dysfunctions developed. In 1982 Pepe and colleagues studied clinical predictors of ARDS.[9] They selected eight conditions that were thought to put the patient at risk for ARDS: (1) sepsis syndrome, (2) aspiration of gastric contents, (3) pulmonary contusion, (4) multiple emergency transfusions, (5) multiple major fractures, (6) near-drowning, (7) pancreatitis, and (8) prolonged hypotension. The greatest risk was associated with sepsis syndrome (38%), followed by documented aspiration of gastric contents (30%), and multiple emergency transfusions (24%). The risk approximately doubled with each increase from one to two to three risk factors. They found that risk factors were

more predictive than the injury severity score (ISS) used in this study. Hudson and colleagues studied another cohort of patients who developed ARDS.[10] Again, sepsis syndrome was the greatest risk factor followed by multiple emergency transfusions and then multiple trauma. Secondary factors of risk included the Acute Physiology and Chronic Health Evaluation (APACHE II) score in patients with sepsis and increased APACHE II and ISS scores in trauma patients.

Scoring Systems for Prediction of ARDS

Roumen and colleagues studied the ability of seven scoring systems and sequential lactate concentrations to predict the development of ARDS.[11] Severity systems include the ISS, Trauma Score (TS), Trauma Score and Injury Severity Score (TRISS), Glasgow Coma Scale (GCS), Polytrauma Score (PTS), APACHE II, and Sepsis Severity Score (SSS). By stepwise regression analysis the authors demonstrated that ISS, SSS, and lactate level at day 3 were the most significant variables for predicting development of ARDS. All patients had multiple trauma. Slotman and Quinn evaluated multiple regression modeling for predicting pulmonary dysfunction in critically ill patients with severe sepsis.[12] Modeling equations used physiologic and clinical laboratory measurements, circulating levels of eicosanoids and cytokines obtained when severe sepsis criteria were first met, and organ dysfunction indicators measured at 24, 48, and 72 hours. A PaO_2/FiO_2 ratio of ≤ 150 and lung injury score of ≥ 7 were used as thresholds. Multivariate prediction of the onset of pulmonary dysfunction in patients without lung dysfunction at baseline was highly sensitive but lacked specificity. When multivariate prediction was used for continued lung dysfunction in patients with lung dysfunction at baseline, it was a poor predictor of PaO_2/FiO_2 changeover time, lacking both sensitivity and specificity. Although the sensitivity and specificity for predicting a lung injury score of ≥ 7 was poor at 7 hours, it increased at 48 hours and became highly sensitive and specific when predicting 72-hour changes.

Specific Serum Factors as Predictors

The ability of serum ferritin to predict ARDS seems rational, as proinflammatory cytokines increase ferritin synthesis as it relates to increased oxidative stress (patients at risk for ARDS might liberate iron from ferritin, thus accelerating toxic hydroxyl radical [·OH] formation). Using this hypothesis to guide their experimented design, Connelly et al. demonstrated a correlation between ferritin levels and being at risk for ARDS.[13] Donnelly and colleagues demonstrated that within minutes of a trauma event there is evidence of enhanced neutrophil degeneration as measured by elevated levels of immunoreactive neutrophil elastase in the peripheral blood.[14] This elevation correlates with the degree of subsequent lung injury. Douzinas studied transpulmonary gradients of cytokines and lactate and demonstrated an increase in these measurements across the pulmonary vascular bed in patients with multiple organ failure (MOF) that included ARDS, whereas there was a drop in levels in patients with MOF that included hepatic injury but not ARDS.[15] This supports the concept of lung production of cytokines and lactate in patients with ARDS and clearance in other non-ARDS states of multiple organ dysfunction. Roumen et al. demonstrated that the concentration of lipofuscin as a measurement of oxidative stress correlated positively with the development of ARDS.[16]

Predictors of Mortality

Table 36.1 summarizes 12 articles published between 1985 and 1998 that demonstrated predictors of mortality for patients with ARDS.[17–26]

Radiologic Assessment

Chest radiographic infiltrates develop almost immediately after the onset of gas-exchange abnormalities of ARDS. The early occurrence of bilateral, symmetric, patchy, dense peripheral infiltrates, predominantly acinar in appearance, is progressively replaced by a diffuse ground-glass appearance. Substantial asymmetry may be seen in the presence of preexisting lung disease (bullae, pulmonary emboli) or if the patient has had a decubitus. Barotrauma in SIRS-induced ARDS is most commonly observed in ARDS during the chronic support phase (weeks 1–4). In patients who demonstrate a path of resolution of ARDS following reversal of the initial insult, radiographic densities tend to reverse over 10–14 days. Some patients, however, develop progressive disease despite apparent control of the triggering process. Most ARDS survivors show near-normal pulmonary function and a near-normal radiographic appearance by 1 year after resolution of ARDS. A smaller proportion of survivors, 20–25%, have both residual fibrosis and persistent significant pulmonary function abnormalities (most notably a diffusion abnormality and restrictive defect).

The portable chest radiograph has limited reliability of radiographic information but is usually all that is available for critically ill patients with ARDS. Variations in technique from day to day can have a significant impact on observer interpretation of improvement or worsening of infiltrates. Attempts to standardize technique as much as possible are desirable. Diuresis tends to alleviate infiltrates, and volume overload worsens infiltrates independent of improvement or worsening of the underlying ARDS. Chest computed tomography (CT) may offer significant advantages in patients with ARDS. It affords improved evaluation of the pleural space (pneumothorax and pleural effusion) and identification of discrete parenchymal abnormalities. It also assists in proper chest tube positioning. It may, however, be a risk to the patient during transport to the radiology department.

Management of ARDS Due to Severe SIRS

General Management Principles

Fluid Balance

In the absence of a need for high left ventricular preload to maintain oxygen delivery it is desirable to maintain a low

TABLE 36.1. Predicting Mortality in Patients with ARDS.

Study	Year	No. of patients	Studied	Results
Montgomery[16]	1985	277 Consecutive patients with risk factors for ARDS, 47 developed ARDS	Mortality in ARDS versus non-ARDS ICU patients	68% Mortality in ARDS patients and 35% in controls; 16% of ARDS deaths due to irreversible respiratory failure; most late deaths due to severe sepsis.
Russell[17]	1990	40 ARDS patients	Oxygen delivery, oxygen consumption, left ventricular preload	Survivors of ARDS had greater oxygen delivery and oxygen consumption than nonsurvivors; greater oxygen delivery appeared related to higher stroke volume index due to greater LV end-diastolic volume.
Suchyta[18]	1992	215 ARDS patients	Cause of ARDS, organ dysfunction, demographics	Deaths of 40% of patients were directly related to respiratory failure. MODS, sepsis, and age increased the chance of mortality from ARDS.
Clark[19]	1995	117 ARDS patients, 6 healthy controls	Studied type III procollagen peptide	Increased levels of type III procollagen in BAL fluid was strongly associated with fatal outcome independent of other variables.
Donnelly[20]	1996	28 ARDS patients, 9 ventilated non-ARDS controls	TNF, IL-1β, IL-8, IL-10, IL-1 receptor antagonist	Low concentration of antiinflammatory cytokines (IL-10, IL-RA) and not high concentrations of proinflammatory cytokines are associated with higher mortality in ARDS.
Headley[21]	1997	34 ARDS patients with conventional treatment and 9 with glucocorticoid therapy for fibroproliferative ARDS	Clinical variables, etiology of ARDS, and inflammatory cytokines (TNF, IL-1, IL-2, IL-4, IL-6, IL-8) in plasma and BAL fluid	Plasma inflammatory cytokine levels but not clinical criteria or precipitating cause of ARDS correlated with patient outcome.
Milberg[22]	1995	918 ARDS patients	Fatality rates by etiology of ARDS and age	Significant decrease in fatality rates predominantly in patients younger than 60 years and those with severe sepsis as etiology. Overall fatality rates decreased to 36% in 1993.
Abel[23]	1998	ARDS patients 41: 1990–1993 78: 1993–1997	Mortality 1990–1993 (period 1) compared to 1993–1997 (period 2) with relation to age, pulmonary physiology, and severity score	Between periods 1 and 2 mortality decreased from 66% to 34%. Postulated to be multifactorial and attributable to general patient management strategies and use of new therapeutic strategies for ARDS. During period 2 the APACHE II score and PaO_2/FiO_2 predicted survival.
Zilberberg[24]	1998	107 Consecutive ALI patients	Studied chronic disease, age, severity of illness, lung injury score, etiology, preceding nonlung organ dysfunction	Predictors of death were age >65, organ transplantation, HIV infection, cirrhosis, active malignancy, and sepsis.
Hudson[10]	1995	695 Patients	Patients with risk factors who developed ARDS vs. those who did not develop ARDS	Overall mortality with ARDS was 62% in those who developed ARDS vs. 19% in those who did not develop ARDS; with trauma 56% vs. 13%; with sepsis 69% vs. 49%.

ICU, intensive care unit; TNF, tumor necrosis factor; IL, interleukin; LV, left ventricular; BAL, bronchoalveolar lavage; ILRA, interleukin receptor antibody; ALI, acute lung injury; HIV, human immunodeficiency virus.

normal capillary pressure in ARDS due to severe SIRS. Hypovolemia should be avoided. Keeping the patient "a little on the dry side" may be associated with a better prognosis.[26] Maintaining a low wedge pressure at the expense of compromising oxygen delivery and organ perfusion, however, is inappropriate. Adequate urine output is usually a good indicator of adequate left ventricular preload.

Increased Airflow Resistance

Airflow resistance may be elevated in patients with ARDS. If airways resistance is increased to a clinically significant degree (evidenced by a large difference between peak and plateau airway pressures not explained by endotracheal tube resistance) or if there is wheezing at the time of physical examination, aerosolized bronchodilator therapy should be considered.

Cardiovascular Support

Increased levels of circulating cytokines have been reported in severe SIRS, and the hemodynamic profile may be the same as that of severe sepsis (increased cardiac output with decreased systemic vascular resistance). The presence of this profile therefore does not necessarily imply sepsis. In ARDS patients who might require vasodilator therapy for other indications, it should be remembered that some vasodilators (nitroglycerin and nitroprusside) have been associated with significantly increased shunting in low ventilation–perfusion areas, leading to significant drops in PaO_2. Cardiac output may also become compromised with treatment of ARDS owing to a combination of high intrathoracic pressure compromising right ventricular filling and increased pulmonary vascular resistance producing right heart dysfunction.

Prevention and Diagnosis of Pneumonia

Ventilation-acquired pneumonia (VAP) is a leading cause of morbidity and mortality in patients with ARDS. The primary risk factors are the presence of the endotracheal tube and the weakened capability of the lungs (and of the patient in general) to deal with bacterial invasion. Although no prospective controlled trials have definitively established clinical outcome differences, there are data, especially in surgical ICU patients, to indicate the ability of selective gut decontamination to decrease the incidence of pneumonia.[27,28] The trade-offs are the possibility of developing resistant organisms and the cost of therapy. Likewise, continuous aspiration of subglottic secretions has also been shown to decrease the incidence of VAP by decreasing the chronic microaspirations around the cuff of the endotracheal tube.[29]

Diagnosing VAP is difficult because patients with ARDS have baseline bilateral infiltrates and frequently other vital sign abnormalities seen with pneumonia. The use of semiquantitative cultures has been advocated by investigators[30,31] but it is controversial especially when patients are already on antibiotics.[32,33] Cutoffs for supporting the diagnosis of pneumonia are typically $\geq 10^3$ colony counts after fiberoptic bronchoscopy (FOB) with a protected catheter brush and $\geq 10^4$ colony counts for FOB. The use of quantitative cultures from blind endotracheal tube aspirates may be a less expensive option than FOB.[32]

Other Therapies to Decrease Morbidity Associated with ARDS and Prolonged Mechanical Ventilation

Patients with ARDS should receive prophylaxis for deep vein thrombosis with some combination of low dose heparin and intermittent compression devices based on the risk for bleeding and additional risks for thromboembolic disease. Enteral nutrition should be instituted on day 1 unless absolute contraindications exist (mechanical obstruction, mesenteric ischemia). Promotility agents and postpyloric placement of the feeding tube may facilitate success. The use of total parenteral nutrition (TPN) should be considered for enteral feeding failures, although the ability of TPN to alter outcome is controversial.[34]

Mechanical Ventilation: Lung Protection Strategy

Minimal (Optimal) Positive End-Expiratory Pressure

The lower inflection point is the midpoint of the transition from the flat portion of the pressure–volume curve to the steeper, more compliant area. With ARDS this point typically represents an area where lung units (alveoli) are collapsing at end-expiration and reopening during the next inspiration. When this is allowed to occur, animal studies suggest that a shearing force is exerted on the endothelial and epithelial cells in collapsed lung that is adjacent to an open lung.[35] It is expected to produce further lung injury. During early ARDS the application of that level of positive end-expiratory pressure (PEEP) at or slightly above the lower inflection point to prevent collapse of acinar units seems reasonable to protect the lung from shear force injury. Each breath would begin on a steeper portion of the pressure–volume curve, leading to improved compliance. The lowest PEEP that gives the best compliance is typically regarded as the optimal PEEP.[36] This PEEP would be expected to maximize recruitment of collapsed alveoli and be assumed to maximize oxygenation from PEEP effect on lung recruitment. In hypoxemic ARDS patients, oxygenation can be increased by optimizing PEEP, increasing mean airway pressure, raising FiO_2, or increasing alveolar ventilation. The latter two items are the least efficient mechanisms. Higher PEEP levels, if resulting in improved oxygenation, may be doing so by increasing mean airway pressure only. Early in the ARDS disease process, sufficient total PEEP that prevents tidal closure of alveolar units (usually 8–15 cmH_2O) may therefore improve compliance and oxygenation as well as decrease injury from repeated opening and closing of unstable lung units.

The lower inflection point (LIP) can be located by constructing a static pressure–volume curve (requires patient paralysis), or it may be inferred by using pressure-controlled ventilation to ascertain the lowest PEEP value that gives the highest tidal volume with a fixed pressure application. This is true only if the inspiratory time is prolonged enough to ensure a no-flow state at

end-inspiration and if the applied inspiratory pressure is low enough to avoid the upper deflection zone (see discussion to follow). More frequently, PEEP is titrated to the value between 8 and 15 cmH_2O that provides the best oxygenation. Another approach is to increase the PEEP based on FiO_2 requirements using PEEP levels of 8–18 cmH_2O as FiO_2 requirements increase between 0.4 and 1.0.

Limiting Alveolar Overinflation

Animal studies suggest that lung injury may be due to alveolar hyperinflation, even if barotrauma does not occur.[37] This injury is called "volutrauma." Understanding volutrauma necessitates understanding the forces determining alveolar inflation and their relation to inspiratory plateau pressure (IPP), the best readily available correlate of transalveolar pressure, the true determinant of alveolar distension. Inflation of alveolar units beyond total lung capacity has been shown to produce hemorrhagic edema in animal lungs. An IPP of 35 cmH_2O is thought to approximate total lung capacity in normally compliant lungs. CT scans of patients with ARDS show that the upper portions of nondependent lung are almost normal in appearance and would be expected to have near-normal compliance.[38] Therefore ARDS patients mechanically ventilated with IPP > 35 cmH_2O are at risk for volutrauma. Using >35 cmH_2O IPP as a cutoff for the risk of volutrauma assumes the presence of normal pleural space, a normal chest wall, and normal abdominal compliance. Therefore in the presence of an edematous chest wall, massive ascites, or large bilateral pleural effusions, a considerably higher IPP may be necessary to reach alveolar distension equal to total lung capacity.[39] Overinflation of lungs is associated with decreased compliance; and as overinflation is approached and exceeded, an upper deflection zone is created on the pressure–volume curve.

Ventilatory strategy can be developed to limit peak alveolar pressure. Measurement of the IPP requires delaying expiration at the end of inspiration (inspiratory hold), allowing pressure to equilibrate in the lung at end-inspiration. This measurement is possible on most modern mechanical ventilators. Lung protective strategy involves the selection of smaller tidal volumes, directly setting it on volume-cycled ventilators or lowering the delivered pressure on time-cycled ventilators. It must be remembered that although the risk of volutrauma (and barotrauma) is defined by the IPP level, it is the increase or decrease in tidal volume that changes this value. Decreasing tidal volume results in a decrease in alveolar ventilation, an increase in $PaCO_2$, and a decrease in pH, which explains the derivation of the name "permissive hypercapnia" as a route to lowering IPP.[40,41] So long as the decrease in pH is not severe ($\geqslant$ 7.25), hypercapnia does not usually cause clinical problems (exceptions include patients with increased intracranial pressure). The tidal volume can be incrementally decreased (by decreasing the applied pressure or the tidal volume directly) to as low as 6 ml/kg. Rises in $PaCO_2$ of 1 mmHg/hr are usually well tolerated so long as the pH remains at 7.25 or higher. In addition, the renal response to $PaCO_2$-induced decreases in pH is to retain bicarbonate and over time allow greater reductions in tidal volume at the same pH. The use of iatrogenic metabolic alkalosis to allow more aggressive lowering of the tidal volume in ARDS patients is controversial (although in general it is supported for permissive hypercapnia in those with severe status asthmaticus).

The strategy of limiting the IPP by decreasing the tidal volume directly with volume-controlled ventilators or indirectly with pressure-controlled ventilators results in a decrease in mean airway pressure. A decrease in mean airway pressure may be associated with a fall in PaO_2, which can usually be countered by holding the tidal volume constant and increasing either the inspiratory time or the rate. Either of these maneuvers increases the mean airway pressure without raising the IPP so long as auto-PEEP is not induced. The inspiration/expiration ratio may be increased to more than 1:1 (inverse ratio ventilation). Auto-PEEP is defined as the positive recoil pressure at end-expiration when there is insufficient time for the lung to return to its functional residual capacity. It is common in patients with chronic obstructive pulmonary disease or with one-lung ventilation.

Clinical Trials

Two clinical trials have been published in peer review journals that target lung protection strategy for potential benefit in ARDS. The first of these studies, by Stewart and colleagues, targeted prevention of overinflation of lung units by utilization of permissive hypercapnia.[42] This study evaluated ventilation strategy to prevent barotrauma in patients at high risk for ARDS. A total of 120 patients were randomized, 60 to each group. Tidal volumes were 7.2 ml/kg in the limited-ventilation group, and 10.8 ml/kg in the control group. Peak inspiratory pressures were 23.6 in the limited-ventilation group and 34.0 in the control group. The incidence of barotrauma, mortality, and highest multiple organ dysfunction scores were the same in the two groups. Paralytic agents were used more frequently in the limited-ventilation group, and dialysis for renal failure was instituted more often. The other two studies (presented in abstract form) also failed to show benefit of limiting inspiratory plateau pressure with use of permissive hypercapnia in ARDS.

The second study, by Amato and colleagues, looked at the effect of protective ventilation strategy on mortality in ARDS.[43] This study, however, targeted not only limitation of inspiratory plateau pressure but also institution of minimal PEEP targeted at the lower inflection point. A total of 53 patients were included in the study: 29 in the protective ventilation group and 17 controls. Mortality at 28 days was 38% in the lung protection group and 71% in the conventional ventilator group. Rates of weaning from mechanical ventilation favored the protective ventilation group by 66% versus 29%. Rates of barotrauma were 7% in the protective ventilation group and 42% in controls. The difference in survival to hospital discharge, however, was not significant, with 45% mortality in the protective ventilation group and 71% in the conventional

TABLE 36.2. Consensus Conference Recommendations for Goals of Ventilatory Management.

1. Ensure appropriate O_2 delivery and sufficient CO_2 removal.
2. Minimize oxygen toxicity: take aggressive steps to lower fraction of FiO_2 when $FiO_2 > 0.65$.
3. Target PEEP toward obliteration of lower inflection point. Use the lowest mean airway pressure that accomplishes oxygenation goals. Full PEEP effects may not be immediately realized.
4. Strategies that keep IPP ≤ 30–40 cmH_2O should be employed.
5. Prevent atelectasis: periodically employ higher volume, longer-duration breaths to forestall atelectasis.
6. Use sedation/hyperanalgesic drugs judiciously and avoid paralytic agents if possible. If paralytic agents are required, use should be as brief as possible and the depth of blockade periodically assessed.

PEEP, positive end-expiratory pressure; IPP, intermittent positive pressure.

ventilation group ($p = 0.37$). This small study, although encouraging for use of a combination of minimal PEEP and limitation of overinflation, needs validation with additional studies. It should also be noted that 71% mortality in the conventional ventilation group is high and is the reason for the difference between the two groups.

Preliminary data from the U.S. National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trial Group study on lung protection strategy in ARDS were recently presented at the annual meeting of the American Thoracic Society. The data revealed a significant reduction in mortality with the 6 ml/kg tidal volume arm of the study compared to the 12 ml/kg arm. Both groups had PEEP titrated upward relative to the severity of hypoxemia. The American-European Consensus Conference on ARDS (Part 2) current recommendations are listed in Table 36.2.[44]

Inverse Ratio (Reverse I:E) Ventilation

A typical inspiratory/expiratory (I:E) ratio selection for mechanical ventilator support is 1:2. The I:E ratio is determined by how much of each minute is required for inspiration; what is left is the expiratory time. Inspiratory time with volume-cycled ventilation is determined by peak inspiratory flow, rate, and tidal volume and with time-cycled ventilation (pressure control) by rate and the direct setting of the inspiratory time for breath delivery. Patients with ARDS require little expiratory time because of the decreased compliance and associated increase in elastic recoil of the lungs. An I:E ratio of 1:1 or higher is feasible in this patient group.[45–47] A potential advantage of such an I:E ratio would be to allow longer inspiratory times to facilitate better filling of noncompliant areas of the lung with prolonged time constants for filling. By increasing the inspiratory time the mean airway pressure, a primary determinant of oxygenation, is also increased. The use of inverse-ratio ventilation to increase mean airway pressure is an option to increase the mean airway with higher inflation pressures, which may be associated with less volutrauma and barotrauma. This mode of ventilation may be tried in patients who cannot be oxygenated with conventional mechanical ventilation and PEEP or in the presence of prohibitively high peak airway pressures. Inverse ratios of up to 3:1 have been utilized. Concerns with inverse-ratio ventilation include barotrauma due to excessive auto-PEEP, hemodynamic compromise due to excessive auto-PEEP or increases in mean airway pressure, and patient tolerance.

High-Frequency Jet Ventilation

High-frequency jet ventilation delivers small tidal volumes (1–5 ml/kg) at rates of 60–3600 cycles per minute. It would be predicted to offer ventilation advantages by ventilating between lower and upper inflection points of the pressure–volume curve in patients with severe ARDS. Thus far no ARDS trials in adults have shown clinical outcome benefit.

Extracorporeal Gas Exchange

Extracorporeal gas exchange theoretically separates oxygenation (extracorporeal membrane oxygenation, or ECMO) and extracorporeal carbon dioxide removal (ECO_2R), although overlap occurs as it relates to clinical usage.[48] During ECMO a high partial pressure of oxygen on one side establishes a concentration gradient for diffusion of oxygen through a semipermeable membrane. Adequate oxygen delivery depends on high blood flow through the circuit. Effective ECO_2R is accomplished when gas flows are high across the membrane relative to blood flow because of the high solubility of CO_2 in blood. Systemic anticoagulation during extracorporeal gas exchange is essential. Extracorporeal gas exchange is morbid, cumbersome, and costly; and it is not recommended for routine use in ARDS patients. Problems encountered include blood loss related to anticoagulation, thrombocytopenia, and a need for frequent patient monitoring. Although there is justifiable enthusiasm for using the technique in infants and children, the results are not as impressive as in adults. Advanced ARDS responds poorly. It seems appropriate to consider it salvage therapy (patients not responding to other therapy). New methods of intracorporeal gas exchange such as the intravenous oxygenation device (IVOX) have also been disappointing thus far.

Prone Positioning

The CT scans obtained in patients with severe ARDS reveal severe basilar atelectasis and consolidation. Ventilation is therefore primarily directed to the more compliant nondependent areas of the lung. Significant perfusion, however, still goes to the more dependent atelectatic lung areas. Ventilation–perfusion (V/Q) matching is therefore poor, with the presence of low V/Q and shunt areas. The primary benefit of prone positioning demonstrated in some patients appears to be a shift from the previous nondependent open areas of lung to a dependent area where perfusion would be better, thereby improving V/Q matching. One could also postulate that reversal of the dorsal atelectasis would occur owing to improved drainage in the nondependent position. Atelectasis and consolidation

would be expected to shift to the now-dependent anterior regions; thus a rationale for rotating the patient back and forth between prone and supine positions has been offered.

The normal smaller size of dependent alveoli relative to nondependent alveoli at functional residual capacity predisposes the lower dependent lung regions to atelectasis in the presence of disease. This gradient may be less severe in the prone position than in the supine position because of differences in the pleural pressure gradient.

In addition, teleologically there may be a better distribution of blood flow relative to ventilation in the prone position. This is because dorsal blood flow may be better preserved than ventral blood flow in the nondependent position. Studies indicate that this is the most likely reason for the improvement in oxygenation, especially as consolidation of the new dependent area and aeration of the new nondependent area occur rapidly.

Prone positioning has been shown to improve oxygenation in some patients.[49–51] If prone positioning is to be used, the earlier the better. With the initial turning to the prone position, oxygenation may temporarily deteriorate prior to improving. Not all patients improve with prone positioning. Prone positioning is difficult for maintenance of lines, tubes, and monitors. Pressure points are problematic, and both shoulders and pelvis should be cushioned with pillows.

Inhaled Nitric Oxide

When inhaled as a gas at low levels, nitric oxide (NO) selectively dilates the pulmonary circulation and may offer physiologic benefit in patients with ARDS.[52–54] Significant systemic vasodilation does not occur because NO is inactivated by rapidly binding to hemoglobin. Furthermore, in patients with ARDS inhaled NO produces greater vasodilation in areas of well ventilated lung units and may "steal" blood flow away from poorly ventilated regions, creating better V/Q matching. This reduces intrapulmonary shunting and improves arterial oxygenation. In patients with ARDS, inhaled NO reduces pulmonary hypertension and improves arterial oxygenation without reducing systemic arterial pressure. Tachyphylaxis due to inhaled nitric oxide (iNO) has not been observed. Although additional chronic toxicology studies are needed, significant pulmonary toxicity has not been observed at inhaled low concentrations. Methemoglobin is not clinically elevated at these concentrations. NO_2 is formed when NO interacts with oxygen, and NO_2 levels in the inspiratory limb are typically monitored. Inhaled NO improves oxygenation in most patients with ARDS.[55] The rationale for iNO therapy is that an improvement in PaO_2 would be associated with decreased mechanical ventilation-related lung injury. In addition, the predominance of animal data and one human study suggests an antiinflammatory effect of inhaled NO that could offer potential benefit in humans.[56–58] Because inhaled NO decreases the increased pulmonary vascular resistance in ARDS, it also decreases pulmonary capillary pressure and could decrease capillary leak.[59]

The first double-blind, placebo-controlled clinical trial of inhaled NO in ARDS was completed in 1995.[55] This multicenter study enrolled 177 patients who met the American-European consensus definition of ARDS [PaO_2/FiO_2 200 mmHg (26 kPa)]. Patients were randomized to inhaled NO at concentrations of 1, 1.25, 5, 20, 40, or 80 ppm. Investigators agreed to guidelines for prioritizing mechanical ventilatory support. Attempts to discontinue the treatment gas were made when the FiO_2 was ≤0.4 and PEEP was ≤5 cmH_2O. In most patients the etiology of ARDS was pneumonia or aspiration. Mechanical ventilation was held constant over the first 4 hours of treatment to evaluate the acute physiologic effects of NO. Approximately 60% of patients receiving inhaled NO met the defined criteria for a response (PaO_2 increase of >20%). By 4 hours, 24% of placebo patients also met the criteria for response. The response rate varied considerably over time and was not associated with outcome measures. Overall mortality was 30% for placebo and pooled inhaled NO groups. Additional outcome parameters evaluated include the number of days alive after reaching oxygenation criteria for extubation, number of days alive and off mechanical ventilation, and the percent of patients alive and off mechanical ventilation at day 28. In terms of the percent of patients alive and off mechanical ventilation at day 28, there were no significant differences noted except for a difference (by post hoc analysis) between the placebo group and the 5 ppm group. There were no significant differences in rates of adverse events across the placebo and the inhaled NO groups.

An open, randomized, parallel group study was performed at 43 sites in Europe; it was stopped in 1997 before full enrollment was completed.[60] A total of 267 patients with acute lung injury (ALI) and unilateral or bilateral pulmonary infiltrates were recruited based on criteria of intubation and mechanical ventilation for 18–96 hours, PaO_2 < 165 mmHg (22 kPa), and PEEP ≥ 5 cmH_2O. Patients were randomized to treatment groups based on their response to 2, 10, and 40 ppm NO inhaled for 10 minutes. An increase of PaO_2 of ≥25% on any dose resulted in 180 responders being randomized to conventional treatment ($m = 87$) or inhaled NO treatment ($m = 93$). The concentration of NO used was the lowest clinically effective dose as determined by the physician. Most patients received 10 ppm NO. The primary endpoint of ALI reversal [PaO_2/FiO_2 > 210–225 mmHg (28–30 kPa)] in preliminary reports was 60% in both treatment groups. Additional endpoints of survival and percent of patients alive and off mechanical ventilation of 30 days were not significantly different between conventional and inhaled NO therapy.

A multicenter, double-blind study of inhaled NO was also completed in France in 1997.[61] A total of 203 patients were enrolled in 24 centers based on Murray score of 2.5–3.0 after therapeutic optimization for 24 hours. Patients received placebo (N_2) or inhaled NO 10 ppm. One shift of gas was allowed for objective deterioration. Patients were weaned from the treatment gas when the PaO_2/FiO_2 was >250 mmHg (33 kPa) on FiO_2 1.0 for at least 4 hours. Preliminary results showed that the primary endpoint of weaning from ventilatory support at 28

days was reached in 31% with inhaled NO and 34% with placebo. Inhaled therapy was discontinued in 62% receiving inhaled NO and 56% receiving placebo. Mortality was not significantly different between the treatment groups.

A case series of 10 consecutive patients with ARDS that developed after pulmonary resection treated with inhaled NO (10–20 ppm) demonstrated significant improvement in oxygenation and good outcome.[62] Although inhaled NO improves right ventricular function in ARDS, it does not typically produce an increase in cardiac output.[63] Although not recommended for routine use in ARDS, inhaled NO should be considered for salvage therapy in patients not responding to traditional ventilation therapy. Other inhaled vasodilators, prostaglandin E_1, and prostaglandin G_2 have also been demonstrated to improve PaO_2 in patients with ARDS.[64,65] No large clinical trials have been performed to judge the effect of these agents on clinical outcome.

Partial Liquid Ventilation

Partial liquid ventilation consists of using a perfluorocarbon as a vehicle to transfer oxygen to blood and eliminate carbon dioxide in patients with severe ARDS.[66] Perfluorocarbon has relatively high density and low surface tension, and it is an efficient carrier of oxygen and carbon dioxide. Partial liquid ventilation is employed by filling the lungs to functional reserve capacity with perfluorocarbon followed by conventional mechanical ventilation of ARDS. The high density and low surface tension of perfluorocarbon appear to enhance recruitment of atelectatic lung regions. This produces a better match between pulmonary blood flow, which is primarily dependent, and ventilation. At the same time blood may be displaced to the better aerated nondependent portion of the lung. Other potential benefits of partial liquid ventilation include mobilization of debris and a possible direct antiinflammatory effect. Complications include the possibility of mucous plug formation and pneumothorax. Clinical trials have thus far been disappointing

Status of Innovative Pharmacologic Therapy

No innovative pharmacologic therapies are currently considered standard therapy, despite much interest and many clinical trials. Although clinical trials using steroids during the early phase of ARDS failed to show any benefit, some investigators now advocate the use of steroids in the later stages of ARDS, the so-called fibroproliferative phase, to decrease progression to fibrosis. Toward the end of the first week of ARDS, nonsurvivors (compared to survivors) have histologic evidence of more intense inflammatory and fibrotic activity with maladaptive lung repair.[67] Furthermore, in patients with persistent ARDS compatible with an overly exuberant fibrotic response, persistently high cytokine levels can be demonstrated in blood and BAL fluid.[68] A single-center study, somewhat handicapped by small numbers (24 patients), significant crossover, and sophisticated statistical analysis, demonstrated rather profound results in favor of steroid treatment for patients with "unresolving ARDS."[69] Although results from this trial are promising, larger clinical trials are needed to validate this therapy.

Although ARDS may have normal amounts of surfactant, it is often dysfunctional. The potential benefit of surfactant replacement includes reduced airway pressures, improved ventilation, and reduced instances of nosocomial pneumonia. Clinical trials in adults with ARDS thus far have failed to show a significant impact of exogenous surfactant on clinical outcome.[70,71] Clinical research continues in this area.

Acetylcysteine, an oxygen scavenger, has been studied in clinical trials of ARDS and has not been shown to have an impact on clinical outcome.[72] Nonsteroidal antiinflammatory drugs, such as ibuprofen and indomethacin, inhibit prostaglandin pathways. A clinical trial in ARDS did not show benefit in clinical outcome.[73] Finally, antiendotoxin and anticytokine therapy might be expected to ameliorate ARDS by decreasing the cytokine and secondary mediator response. Thus far, multiple clinical trials in severe sepsis have not indicated any improvement in clinical outcome related to ARDS.[74]

Clinical trials in ARDS patients have been judged unsuccessful or as failures based on endpoints of mortality or days alive and off assisted ventilation. Some argue that these endpoints are unrealistic and difficult to obtain with most therapies, even if they are beneficial.[75] This position is controversial.[76]

Conclusions

The lung remains the primary affected organ in SIRS. Although the direct contribution of pulmonary dysfunction to mortality is less clear, the inability to quickly transition the patient to liberation from mechanical ventilation has major implications for iatrogenic complications and morbidity during the ICU stay. Much has been learned about the inflammatory milieu that produces and sustains ALI and ARDS. Thus far interventions targeted toward ameliorating that response have been unsuccessful. New therapies and better understanding may yet lead to success in this area. Our understanding of the potential for ventilation-induced lung injury has led to consensus recommendations on ventilation management. Several therapies that are not recommended for routine therapy of ARDS should be considered for salvage therapy. Prophylaxis to avoid iatrogenic complications during the ICU stay is important, as is adequate nutritional support.

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