

Acute Respiratory Distress Syndrome—Two Decades Later

ANTHONY J. CUNNINGHAM, F.A.C.A., F.F.A.R.C.S.I., F.R.C.P.C.

Professor of Anaesthesia, Royal College of Surgeons in Ireland, Dublin, Ireland

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Twenty years have now elapsed since Ashbaugh and Petty first described the syndrome of acute respiratory failure associated with a wide spectrum of clinical conditions. During the past two decades, significant advances have emerged in our understanding of the clinical conditions associated with the syndrome and the pathophysiological changes affecting the alveolar-capillary membrane responsible for the characteristic non-cardiogenic pulmonary edema. Recent data have reaffirmed the notion that mortality rates in ARDS remain in excess of 60 percent, essentially unchanged since the first description of the syndrome, despite all the advances in critical care medicine in the intervening years.

The incidence of ARDS has been difficult to establish because of lack of agreement on precise definition criteria. The lack of agreed definition criteria has hampered evaluation of the natural history of the syndrome, its epidemiology and mortality rates, and the efficacy or otherwise of a variety of therapeutic interventions.

This review will highlight a recent, clinically appropriate, expanded definition of ARDS. New understandings of the roles of sepsis and multi-system organ failure in mortality associated with ARDS will be discussed. Several mediators, both locally in the lung and in the systemic circulation, have been implicated in the pathophysiology of ARDS. This review will discuss the evidence for and against neutrophils, platelets, cytokines derived from mononuclear cells and macrophages, complement, prostaglandins/leukotrienes, oxygen-derived radicals, and a variety of proteases.

Current treatment strategies for ARDS are designed to increase tissue oxygen delivery by increasing arterial oxygen tension and cardiac output while simultaneously attenuating the pulmonary and systemic injury by appropriate pharmacologic and surgical interventions. Recent data advocating pharmacological augmentation of cardiac index and oxygen delivery will be highlighted. The persistently high mortality rates of 60–70 percent in patients with established ARDS have provoked recurring interest in new techniques of providing mechanical ventilation. Most studies have shown, however, that mortality in ARDS patients is attributable mainly to sepsis and multi-system organ failure rather than primarily to respiratory failure. Established and speculative intervention to reduce sepsis and multi-system organ failure associated with ARDS will be featured in the review.

INTRODUCTION

A syndrome of respiratory dysfunction, characterized by severe hypoxemia, patchy bilateral pulmonary infiltrates on chest X-ray, and low pulmonary compliance was described by Ashbaugh and Petty in the *Lancet* in 1967 [1]. The terms “shock lung,” “Da Nang lung,” and others applied to the syndrome in the late 1960s and early 1970s have been replaced by the now universal description of adult respiratory distress syndrome (ARDS). ARDS has become widely used to convey the clinical manifestations of the effects of increased permeability of the alveolar-capillary

Abbreviations: ARDS: adult respiratory distress syndrome CPAP: continuous positive airway pressure DO₂: tissue oxygen delivery ECMO: extracorporeal membrane oxygenation MOF: multi-organ failure PaCO₂: arterial carbon dioxide tension PaO₂: arterial oxygen tension PCWP: pulmonary capillary wedge pressure PEEP: positive end-expiratory pressure

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membrane: i.e., non-cardiogenic pulmonary edema, interstitial and alveolar edema formation, with a normal plasma oncotic pressure.

This review will highlight an expanded definition of ARDS, the clinical conditions associated with ARDS, pathophysiology of the syndrome, the pathogenesis of acute lung injury, and current treatments for ARDS (Table 1).

DEFINITION

Ashbaugh and Petty, in their classic article in 1967, described ARDS as a syndrome of acute respiratory failure, characterized by non-cardiogenic pulmonary edema with severe hypoxemia caused by right-to-left intrapulmonary shunting secondary to atelectasis and air space filling from edema fluid [1]. The chest X-ray showed diffuse pulmonary infiltrates, and there was a decrease in lung compliance; the lungs required higher than normal airway pressures to deliver a normal tidal volume.

Hallmarks of the syndrome have classically been described as:

1. Hypoxemia: PaO₂ less than 8 kPa or 60 mmHg with an FIO₂ of 0.5 or greater
2. New patchy, diffuse, bilateral pulmonary infiltrates on chest X-ray
3. Low pulmonary compliance
4. Normal left ventricular filling pressures: pulmonary capillary wedge pressure (PCWP) < 15 mmHg

The incidence of ARDS has been difficult to establish because of lack of agreement on precise definition criteria for its diagnosis. The differences in the reported incidence of ARDS reflect the various criteria used to establish the diagnosis. U.S. data from the National Heart, Lung and Blood Institute, published in 1977, estimated an annual 150,000 cases of ARDS, with a mortality of approximately 50–60 percent [2]. The U.S. estimate predicted an annual incidence of 60 per 100,000 of the population. A more recent U.K. study predicted an incidence of 5 per 100,000 of the population [3]. A prospective study of a homogeneous population in the Canary Islands reported an incidence of 2–4 per 100,000 population, with a mortality of approximately 70 percent [4].

Recent data [5] and accompanying editorials [6] have reaffirmed the notion that mortality rates in ARDS remain in excess of 60 percent, essentially unchanged since the first description of this syndrome by Ashbaugh and Petty. It seems, however, intuitively obvious to most clinicians that many patients in risk groups such as trauma who develop pulmonary infiltrates and require mechanical ventilation are treated successfully and survive. Two common criteria—hypoxemia refractory to positive end-expiratory pressure (PEEP) and simultaneous normal pulmonary artery occlusion pressure—may have introduced a significant selection bias into the definition of ARDS. The possibility has been considered that entry criteria for ARDS in pub-

lished studies have increasingly selected an atypical population with a high incidence of co-existing multi-system organ failure and an excessively high mortality rate [7].

Much of the controversy concerning ARDS is explained by the lack of a satisfactory definition of the syndrome. The lack of agreed definition has hampered evaluation of the natural history of the syndrome and its epidemiological and mortality data and has limited the study of pathophysiologic mechanisms and new therapeutic interventions.

A major development in defining ARDS has been advanced recently by Murray et al. [8] in their proposed expanded definition of the syndrome. The authors include a semi-quantitative method for scoring acute lung injury derived, in part, from criteria used by other investigators. The scoring involves a four-point system: (1) the impairment of oxygenation is quantified by the ratio of arterial oxygen tension to the fraction of inspired oxygen ($\text{PaO}_2/\text{FIO}_2$); (2) the chest X-ray is scored on the four-point system; if the chest X-ray is clear, then no points are assigned; one to four points are assigned for consolidation in the four lung zones; (3) the respiratory compliance may be measured by applying an end-expiratory hold or plateau and the plateau pressure minus the positive end-expiratory pressure (PEEP) divided by the tidal volume delivered gives the static pulmonary compliance; (4) the PEEP level—the PEEP applied may influence arterial oxygenation and provides some indication of the severity of respiratory failure (Table 2).

Using this four-point scoring system, the aggregate sum of the number of components divided by four is used to classify acute lung injury as mild/moderate ($0.1 < 2.5$) or severe > 2.5 . In addition to quantifying the severity of lung injury, Murray's expanded definition includes an assessment of whether the parenchymal lung injury is acute or chronic and describes the lung injury as being caused by, or associated with, specific clinical disorders.

CLINICAL CONDITIONS ASSOCIATED WITH ARDS

The expanded definition of ARDS proposed by Murray et al. [8] includes assessment of the clinical disorders associated with the development of ARDS. Recent prospective epidemiological studies have identified sepsis syndrome, gastric aspiration, shock, major trauma, multiple transfusion, acute pancreatitis, drug overdose, pneumonia, and near-drowning as being the common clinical disorders associated with the development of ARDS [9]. The risk of developing ARDS increases with the number of clinical disorders that occur in the same patient. In addition, the time course for the development of ARDS after the onset of clinical disorder has been examined. Overall, acute lung injury develops within 24 hours in 80 percent of patients at risk who ultimately develop ARDS. Recent prospective data from Weinberg et al. [10] noted that ARDS developed following sepsis in less than six hours in many patients.

Sepsis

Sepsis is the most common clinical disorder associated with the development of ARDS; 20–40 percent of patients with sepsis syndrome may develop ARDS [11]. The relationship between sepsis and ARDS has been the subject of ongoing studies. The source of infection was usually found in the abdomen on autopsy studies in patients with clinical evidence of infection and positive blood cultures but with an antemortem undetermined site of infection. In contrast, when patients had negative blood

TABLE 2
Expanded Definition of ARDS

| | Value | Score |
|---|-----------------------------|---------|
| 1. Chest radiograph score | | |
| No alveolar consolidation | — | 0 |
| Alveolar consolidation in one quadrant | — | 1 |
| Alveolar consolidation in two quadrants | — | 2 |
| Alveolar consolidation in three quadrants | — | 3 |
| Alveolar consolidation in all four quadrants | — | 4 |
| 2. Hypoxemia score | | |
| PaO ₂ /FIO ₂ | ≥ 300 | 0 |
| PaO ₂ /FIO ₂ | 225–299 | 1 |
| PaO ₂ /FIO ₂ | 175–224 | 2 |
| PaO ₂ /FIO ₂ | 100–174 | 3 |
| PaO ₂ /FIO ₂ | < 100 | 4 |
| 3. Respiratory system compliance score (when ventilated) | | |
| Compliance | ≥ 80 ml/cmH ₂ O | 0 |
| Compliance | 60–79 ml/cmH ₂ O | 1 |
| Compliance | 40–59 ml/cmH ₂ O | 2 |
| Compliance | 20–39 ml/cmH ₂ O | 3 |
| Compliance | ≤ 19 ml/cmH ₂ O | 4 |
| 4. PEEP score (when ventilated) | | |
| PEEP | ≤ 5 cmH ₂ O | 0 |
| PEEP | 6–8 cmH ₂ O | 1 |
| PEEP | 9–11 cmH ₂ O | 2 |
| PEEP | 12–14 cmH ₂ O | 3 |
| PEEP | ≥ 15 cmH ₂ O | 4 |
| The final value is obtained by dividing the aggregate sum by the number of components that were used: | | |
| No lung injury | | 0 |
| Mild-to-moderate lung injury | | 0.1–2.5 |
| Severe lung injury (ARDS) | | > 2.5 |

Adapted from Murray et al. [8]

cultures and clinical sepsis, the autopsy examination revealed the origin of sepsis to be in the lung. Montgomery et al. [12] reported that early and late mortality in patients with ARDS was primarily related to sepsis. Respiratory failure accounted for 10 percent of the deaths in the first three days following the onset of ARDS and only 18 percent of delayed mortality. In contrast, sepsis accounted for 30 percent of the early mortality and 36 percent of the late mortality. Seidenfeld et al. [13] reported survival rates of only 29 percent among 129 patients with ARDS. Sepsis was more common in the non-survivors, and the lung and abdomen were the most common sites of infection. Even with appropriate antibiotic therapy, the outcome of ARDS associated with sepsis was poor.

Aspiration of Gastric Contents

Aspiration of gastric contents is another clinical disorder frequently associated with ARDS. Acid aspiration or Mendelson's syndrome is a potentially preventable, iatrogenic complication of general anesthesia. Many factors predispose to pulmonary aspiration, but the risk may be reduced by the use of regional anesthesia, where appropriate, and by the use of awake endotracheal intubation preceding induction of anesthesia, in the patient population at risk of developing the syndrome. Pre-

TABLE 3
Factors Affecting Outcome in ARDS

| |
|--|
| A. Age at the time of presentation |
| B. The route of development of ARDS |
| 1. Airway |
| 2. Circulation |
| C. The severity of the precipitating illness |
| D. The development of multi-system organ failure |

operative use of H_2^- receptor antagonists to reduce gastric acid production, non-particulate antacids to neutralize gastric acid, and metoclopramide to increase peristalsis and promote gastric emptying should minimize the chances of gastric fluid of low pH being aspirated into the tracheobronchial tree in the perioperative period [14].

Major Trauma

ARDS may develop in trauma victims associated with pulmonary contusion or in patients with severe hypotension requiring multiple blood transfusions. ARDS develops in other trauma patients with the development of sepsis syndrome, several days after the initial presentation. In trauma victims with long bone fractures, fat embolism syndrome and ARDS may develop 24–48 hours later. Mortality rates of 10 percent for ARDS associated with fat embolism have contrasted with up to 90 percent mortality rates in patients developing ARDS following sepsis. ARDS patients with fat embolism syndrome, appropriately treated with mechanical ventilation, should have greater than 90 percent survival rates [15].

Factors Affecting Outcome in ARDS

The clinical disorders leading to the development of ARDS clearly influence the prognosis for recovery. Factors related to mortality in ARDS include: age at the time of presentation; the route of development of ARDS, i.e., via airway or via circulation; the severity of the precipitating illness; the development of multi-system organ failure (Table 3). The Division of Lung Diseases, Heart, Lung and Blood Institute study [12] identified age as a significant factor in mortality. Using the criteria of requirements for FI_{O_2} of 0.5 and intermittent positive-pressure ventilation for 24 hours or longer, mortality rates of 61 percent for patients less than 65 years old and 82 percent for patients more than 65 years old were reported.

Multi-System Organ Failure

The third part of the expanded definition of ARDS by Murray et al. [8] includes the specification of organ system failure other than the lung. The importance of non-pulmonary organ failure has been recognized increasingly in ARDS patients. Dorinsky et al. [17] recently reviewed the incidence of non-pulmonary organ failure in patients with ARDS. Abnormalities were most consistently observed in the kidneys; however, hepatic dysfunction has been reported in as many as 95 percent of patients with ARDS.

Cardiac Dysfunction

The diagnosis of ARDS involves exclusion of cardiogenic causes of respiratory failure. Studies have indicated, however, that up to 20 percent of patients with

TABLE 4
Differential Diagnosis of ARDS

| |
|--|
| Crystalloid overload |
| Left ventricular failure |
| Neurogenic pulmonary edema |
| Aspiration pneumonia |
| Overwhelming viral/bacterial pneumonia |

ARDS have concomitant cardiac disease. Sepsis may be associated with impaired left and right ventricular ejection fraction [18]. Concomitant hepatic failure and ARDS have been associated with especially poor prognosis. Hepatic failure in association with acute lung injury may have up to 100 percent mortality [17].

Renal Impairment

Renal impairment may be the most commonly associated non-pulmonary organ failure in patients with ARDS. Mortality rates of 80 percent with ARDS have been reported if the initial pH remains less than 7.4 following intermittent positive-pressure ventilation, if the initial serum bicarbonate is less than 20 mmol/dl⁻¹, and if the initial concentration of blood urea nitrogen is greater than 23 mmol/l⁻¹. ARDS patients with these findings have an 80 percent mortality compared with a 40 percent mortality in patients with normal serum bicarbonate and blood urea nitrogen [5].

Gastrointestinal, central nervous system, and hematological dysfunction may also commonly be associated with ARDS development.

Differential Diagnosis of ARDS

ARDS must be distinguished from other conditions which give rise to similar X-ray appearances of pulmonary edema, i.e., fluid overload, left ventricular failure, neurogenic pulmonary edema, aspiration pneumonia, and overwhelming viral/bacterial pneumonia (Table 4).

The first clinical sign is usually dyspnea and tachypnea. The earliest laboratory abnormality is usually a decrease in arterial oxygen tension (PaO₂) and possibly a reduced arterial carbon dioxide tension (PaCO₂). As respiratory failure develops, there is a reduction in PaO₂ despite a high inspired oxygen concentration, and there is evidence of pulmonary edema on chest X-ray, with the added development of respiratory acidosis. X-ray changes may be absent during the first 12 hours of the syndrome, and the only finding may be hyperventilation and a reduction in arterial oxygen tension. The earliest X-ray change is usually interstitial edema. As the condition worsens, patchy densities develop and progress to the profuse symmetrical alveolar pattern in both lungs with air-bronchogram appearance.

PATHOPHYSIOLOGY OF ARDS

Acute Phase

Disruption of the alveolar-capillary membrane by a variety of mechanisms, either directly through the airway or indirectly via the bloodstream, has been implicated as the pathophysiological mechanism responsible for ARDS development. In the early phase of acute respiratory failure, patients typically manifest severe alveolar edema, with large numbers of inflammatory cells, primarily neutrophils, in the air spaces and

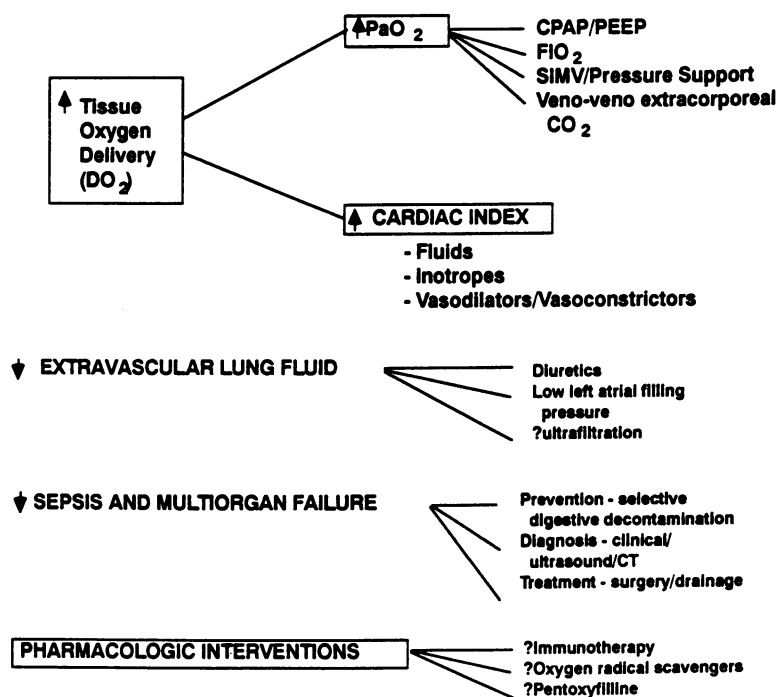


FIG. 1. ARDS
—current therapy.

interstitium of the lungs. Initially, the edema fluid has a high concentration of protein, which is characteristic of an increased-permeability pulmonary edema. In addition, the epithelial injury in the acute phase of ARDS has recently been highlighted. Epithelial injury is now emerging as a very important component of the acute lung injury, partly because injury to the epithelium lowers the threshold for alveolar flooding and results in a substantial deterioration in gas exchange.

Recent data have suggested that the presence or absence of normal alveolar epithelial function, as measured by sequential concentrations of protein in pulmonary edema fluid, may be an important prognostic indicator in ARDS patients [19]. If patients absorb excess alveolar fluid within the first 12 hours after developing pulmonary edema, alveolar epithelial function may remain reasonably intact, and recovery prospects are improved. In contrast, patients who manifest no change in pulmonary edema fluid protein concentration, in the first 12 hours after the onset of mechanical ventilation, may have higher mortality rates. Pleural effusions may be noted in 40 percent of patients with increased-permeability pulmonary edema [11]. Approximately 20–25 percent of the excess lung water in ARDS that accumulates within the first few hours may drain into the pleural space and is cleared from the thoracic cavity by pleural lymphatics. The pleural space is an important route for the clearance of a significant fraction of pulmonary edema fluid.

Subacute Phase

The subacute phase of ARDS occurs approximately from days 5 to 10 after lung injury and primarily involves the interstitium of the lung. Some patients develop an accelerated fibrosing alveolitis. Ultrastructural studies have shown extensive proliferation of the alveolar type II epithelial cells, apparently in response to injury of the

type 1 epithelial cells in the acute phase [20]. There is a pronounced increase in fibroblast and collagen formation in the interstitium. Considerable interest has focused on the role of the fibroblast and epithelial growth factors, which may be released from macrophages or other cells in the lungs, as mechanisms for the responses to acute lung injury. The highest risk of infection appears to be in the first six to ten days after the initiation of ventilation [21]. The destruction of lung tissue results in an impairment of both blood and lymphatic drainage, and the presence of cellular debris and plasma in the airway, with impaired mucociliary transport, may predispose to secretion retention and the development of pneumonia.

Chronic Phase

Lung destruction may occur during the chronic phase of ARDS 10–14 days after the onset of the syndrome. Varying degrees of lung destruction, emphysema, and pulmonary vascular obliteration, in addition to areas of fibrosis, may develop. In this chronic phase, patients may have lesser degrees of oxygenation impairment and lesser PEEP requirements; these patients continue to have high dead space and high minute ventilation requirements. Lung compliance may be decreased secondary to pulmonary fibrosis and diminished surfactant synthesis.

Pulmonary function studies of ARDS survivors have demonstrated that many patients who recover from the syndrome have normal to near-normal pulmonary function. Some patients with no previous history of reactive airway disease or no prior history of smoking may, however, develop reactive airway disease after recovery from ARDS [22]. Studies of ARDS survivors have indicated that patients who were bacteremic during their illness had a greater decrease in their diffusion capacity following recovery. There is no correlation between recovery of pulmonary function and the duration of mechanical ventilation, the inspired concentration of oxygen utilized, and the period for which supplementary oxygen was required. Other studies have noted a correlation between post-ARDS pulmonary function and the maximal pulmonary artery pressures, the lower pulmonary compliance, and the maximum PEEP required during the patient's illness [23].

PATHOGENESIS OF ARDS

Several mediators, both locally in the lung and in the systemic circulation, have been implicated as being responsible for the pathophysiological changes associated with ARDS (Table 5). Much recent interest has focused on the complex interaction of circulating and resident lung cells in the pathophysiology of the syndrome. Interest has centered on the role of neutrophils, platelets, cytokines derived from mononuclear cells and macrophages, the complement system, prostaglandins/leukotrienes, oxygen-derived radicals, and a variety of proteases.

Neutrophils

Neutrophil function may be divided into four phases: adherence, chemotaxis, phagocytosis, and triggering of post-phagocytic intercellular events designed to destroy ingested microorganisms [11].

There is considerable evidence to implicate the neutrophil in the initial lung damage in patients who develop ARDS. Proponents of neutrophil-related lung injury claim that peripheral leucopenia is associated with ARDS [24] because of complement-activated neutrophil accumulation in the lung [25]. Large numbers of

TABLE 5
Pathogenesis of ARDS: Current Postulates

| |
|---------------------------|
| Circulating Cell |
| Neutrophils |
| Platelets |
| Monocytes |
| Resident Lung Cells |
| Alveolar macrophages |
| Intravascular macrophages |
| Epithelial cells |
| Mediators |
| Complement activation |
| Cytokines: |
| Tumor necrosis factor |
| Interleukin 2 |
| Prostaglandins |
| Oxygen-derived radicals |
| Proteases |

neutrophils collect in the lung in the early phases of lung injury. Under these circumstances, neutrophils may be present in a functionally and metabolically activated state. The chemotactic responses of neutrophils in patients with ARDS may be increased when compared with control patients. Activated neutrophils which sequester in the pulmonary circulation may release toxic oxygen free radicals, proteolytic enzymes, and products of arachidonic acid cascade, which damage the pulmonary microvascular endothelial cells and cause the increased permeability of pulmonary capillaries [26].

Other investigators, however, have failed to establish a relationship between leucopenia and the development of ARDS. Investigators have reported the development of ARDS in patients with severe neutropenia after chemotherapy [27]. There may be both neutrophil-dependent and neutrophil-independent mechanisms responsible for the initial lung injury.

Platelets and Disseminated Intravascular Coagulation

Platelet abnormalities and activation of the coagulation cascade have been implicated in the pathogenesis of ARDS. In a study of septic patients at risk for the development of ARDS, a platelet count of less than $100,000 \text{ mm}^{-3}$ was associated with an increased risk of ARDS development. The study also demonstrated significant platelet sequestration in the reticuloendothelial system in these patients [28].

Thrombocytopenia, intravascular microthrombosis, and decreased fibrinolysis have all been implicated in the pathogenesis of ARDS [29]. Depressed fibrinolysis associated with inhibition of plasmin and plasminogen activator have also been reported [30]. Coagulation disorders, including thrombocytopenia and intravascular coagulation, may be associated with ARDS; however, these disorders may also be associated with sepsis and major trauma. Platelet and coagulation abnormalities are not reliable specific predictors for the development of ARDS.

Complement System

Complement activation has been implicated in the pathogenesis of the acute lung injury associated with ARDS. In particular, C3a and C5a, potent neutrophil chemo-

tactic stimulants, have been found in excess quantities in bronchoalveolar lavage fluid obtained from patients with ARDS [31]. The degree of complement activation has been reported to be predictive of the development of ARDS [32]. Other investigators have noted increased concentration of C5a in patients with sepsis, but levels did not predict the development of lung injury. The concentration of C5a may correlate better with hypotension and metabolic acidosis than with the eventual development of acute lung injury [33]. Complement activation may be part of the pathophysiological process during sepsis which leads to systemic and pulmonary endothelial injury but may not be the sole factor responsible for the development of lung injury.

Cytokines

Considerable recent attention has focused on the possible contribution of a number of cytokines in the development of acute lung injury [11]. Tumor necrosis factor, a peptide produced by mononuclear cells in response to endotoxin and interleukin 2, reproduces the physiological changes, e.g., hypotension and metabolic acidosis, associated with septic shock syndrome [34]. The macrophage is probably the principal cell involved in mediating the effects of endotoxin, and the elaboration by macrophages of tumor necrosis factor may be a crucial response to sepsis [35]. Monocytes may also produce a variety of interleukins which exaggerate the inflammatory response. In addition, alveolar macrophages secrete a variety of factors which sequester neutrophils in the lungs, and which may contribute to the development of ARDS [36]. Intravascular pulmonary macrophages may have an important effect in modulating acute lung injury. The release of intracellular products of intravascular macrophages may contribute to the increased pulmonary endothelial and epithelial permeability characteristic of ARDS [11].

Prostaglandins/Oxygen Radicals/Proteases and Other Mediators

Cyclo-oxygenase and lipoxygenase by-products of arachidonic acid metabolism have been extensively investigated as agents mediating the acute lung injury associated with ARDS. Experimental studies have implicated cyclo-oxygenase products in mediating the initial pulmonary hypertension as well as the bronchoconstriction which may occur following endotoxin infusion [37]. Other clinical studies have reported substantial quantities of the lipoxygenase product leukotriene D4 in bronchoalveolar lavage and pulmonary edema fluid of patients with ARDS [38]. The role of prostaglandin in mediating the pathological changes in ARDS may be clarified if studies of prostaglandin metabolism inhibitors indicate a beneficial effect on alveolar gas exchange and morbidity. Preliminary data suggest that ibuprofen, a cyclo-oxygenase inhibitor, produces a modest improvement in oxygenation in some patients with ARDS [38].

Recent studies have focused on the role of oxygen-derived radicals from neutrophils and platelets in the pathogenesis of ARDS and the role of oxygen free radical scavengers in the treatment of the syndrome. In addition to neutrophils and platelets, oxygen free radical production may be associated with high inspired oxygen administration and reperfusion of hypoxic tissues. The anti-oxidants superoxide dismutase, catalase, and glutathione peroxidase may reduce the concentrations of toxic oxygen free radicals and may have a role in the prevention and therapy of ARDS.

A variant of proteolytic enzymes, e.g., elastase, hyaluronidase, and plasminogen activator derived from granulocytes and mononuclear cells, may disrupt the capillary endothelium and increase vascular permeability.

CURRENT TREATMENTS FOR ARDS

The objectives of current treatment strategies in ARDS are to increase tissue oxygen delivery by increasing arterial oxygen tension and cardiac output while simultaneously attenuating the pulmonary and systemic injury by appropriate pharmacologic and surgical interventions.

Increased Oxygen Delivery

In many patients with ARDS, a combination of hypoxemia and decreased cardiac output produces critical reductions in tissue oxygen delivery (DO_2). In ARDS patients, hypotension and low cardiac output may be associated with hypovolemia due to major trauma or PEEP-induced reductions in venous return; decreased myocardial contractility due to pre-existing heart disease or the effect of sepsis on myocardial contractility and sepsis-induced changes in systemic vascular resistance.

Fluid Management in ARDS

The aims of fluid management in ARDS are to maintain adequate organ perfusion and nutrition without increasing pulmonary extravascular fluid which, in turn, may aggravate pulmonary gas exchange.

The factors which influence the choice of intravenous fluid are determined by the differences in hydrostatic pressure between the pulmonary capillary and the interstitial space; the difference in oncotic pressure between these two spaces and the effect of lung injury on the reflection coefficient (which determines the amount of substances of large molecular weight which leak through capillaries) [11]. The most significant treatment option is to maintain low capillary pressures, thereby reducing the hydrostatic transcapillary pressure gradient. This reduction must be commensurate with adequate organ perfusion. Volume expansion with blood, in the first instance, to maintain an adequate hematocrit (approximately 0.4) is the first step in the correction of hypovolemia. Thereafter, colloids are more effective in maintaining circulating blood volume than crystalloids. Of the available colloids, albumen, hetastarch and pentastarch are the longest-acting, while polygeline solutions are short-acting and effectively become crystalloids eight to 12 hours later.

Cardiac Output Augmentation

Pre-existing cardiac disease and sepsis-induced reductions in ventricular ejection fraction may require specific inotropic support. Recent data by Shoemaker [39] suggest that pharmacological augmentation of cardiac index and oxygen delivery, e.g., cardiac index greater than 4.5 l/m^{-2} and increased DO_2 and VO_2 , may reduce cardiorespiratory complications in high-risk surgical patients. Improved oxygen delivery in these patients may improve organ perfusion and thereby reduce the incidence of multi-system organ failure. In other studies, cardiac output and oxygen consumption in patients with sepsis were improved by vasopressor therapy, but mortality was no better than in patients treated with intravenous fluids alone [40]. Further studies to confirm the possible benefit of therapy directed at improving oxygen delivery in patients with ARDS are indicated.

Increased Improving Arterial Oxygen Tension

The persistently high mortality rates of 60–70 percent in patients with ARDS have provoked recurring interest in new techniques of providing mechanical ventilation for patients with ARDS. Most studies have, however, shown that mortality in ARDS patients may be attributed to sepsis and multi-system organ failure rather than primarily to respiratory failure.

Innovations in techniques of mechanical ventilation have included extracorporeal membrane oxygenation (ECMO); high-frequency jet ventilation; pressure-controlled, inverse-ratio ventilation; and, most recently, extracorporeal carbon dioxide removal. Zapol et al. [41] in the ECMO study published in 1979 compared a control group treated with conventional mechanical ventilation with ECMO-treated patients who received lower tidal volumes and mean airway pressures. Similar high mortality rates of 90 percent with similar incidence of barotrauma were reported in the two groups. In the early 1980s, high-frequency ventilation was advocated as an alternative to conventional ventilation, partly because lower peak airway pressures could be employed, which might result in less barotrauma and less ventilation-induced lung injury. Subsequent data indicated, however, that significant improvements in oxygenation could be achieved with high-frequency jet ventilation only in association with increased mean airway pressures, which, in turn, had deleterious effects on venous return and cardiac output [42]. In a well-designed prospective randomized study of 309 patients, Carlon et al. [43] noted no significant difference in the total duration of intensive care or survival in patients treated with high-frequency jet ventilation compared with conventional volume-controlled ventilation. More recently, MacIntyre et al. [44] concluded that high-frequency jet ventilation offers no important clinical benefits compared with conventional intermittent positive-pressure ventilation in adult patients with ARDS, with the possible exception of those patients with large bronchopleural fistulae.

Recent interest has focused on the use of pressure-controlled, inverse-ratio ventilation as an alternative to conventional volume-controlled ventilation in patients with ARDS. Tharrat et al. [45] published a retrospective study of the use of pressure-controlled, inverse-ratio ventilation in 31 patients with severe ARDS. This ventilatory technique was reported to be associated with significant reduction in minute ventilation, peak inspiratory pressure, PEEP, and some improvement in arterial oxygenation. There was, however, an overall mortality of 77 percent in the 31 patients with ARDS. A significant increase in mean airway pressure was noted, and pneumothorases developed in six of the 31 patients studied. A recent Italian study reported favorable outcome with veno-veno extracorporeal membrane carbon dioxide removal with low-frequency positive-pressure ventilation in 47 patients with ARDS [46]. Veno-veno extracorporeal membrane carbon dioxide removal is currently the subject of a prospective study centered at the University of Utah in Salt Lake City [47].

CPAP/PEEP

Continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP) are believed to have several therapeutic effects in ARDS. They may reverse progressive alveolar collapse and reduce interstitial edema, thereby improving alveolar gas exchange and increasing arterial oxygen tension. CPAP and PEEP may

effectively increase the functional residual capacity, increase PaO₂, and decrease the magnitude of intrapulmonary shunt [48]. The appropriate methods of CPAP/PEEP delivery are difficult to determine, but decreasing intrapulmonary shunt with increased arterial oxygen tension, improving pulmonary compliance and oxygen transport have all been used to identify the “best PEEP” level [49]. The beneficial effects of CPAP/PEEP are not without potential side effects. Venous return may be decreased because of increased intrathoracic pressure, resulting in decreased cardiac output. Increased mean airway pressure predisposes to barotrauma. The detrimental effects of PEEP are most pronounced in hypovolemic patients.

The appropriate level of PEEP is still disputed. Early initial enthusiasm that suggested improved survival in ARDS with PEEP was subsequently disputed when randomized studies of increased versus moderate levels found no significant differences between the two groups in terms of duration of mechanical ventilation or overall mortality rates [50]. The use of prophylactic PEEP in patients at risk of ARDS also remains controversial. A prospective study of the prophylactic use of 8 cm H₂O PEEP in patients at high risk for developing ARDS proved that such use was of no benefit in preventing acute lung injury [51]. There is no evidence that PEEP hastens the recovery from lung injury, prevents the development of lung injury, or reduces extravascular lung water. Alveolar edema is primarily dissolved by an active sodium transport, which may not depend on the mode of ventilation but on the airway pressure.

The mainstay of current management of ARDS is to maintain the arterial oxygen tension greater than 8 Kpa or 60 mmHg, utilizing as low as possible inspired oxygen concentration, with the judicious use of PEEP and optimum tidal volume.

Pharmacological Interventions

ARDS may be considered as the pulmonary manifestation of multi-organ failure (MOF) syndrome. The death rate for ARDS is closely related to the number of other organ systems that fail. Pharmacological intervention for ARDS may prevent multi-organ failure and, if given to high-risk patients, may also prevent the occurrence of ARDS.

Corticosteroids have been the most widely used drugs in ARDS because of their established anti-inflammatory properties [52]. These drugs have been shown to reduce lung injury in experimental studies. Corticosteroids have been reported to improve outcome in patients with fat embolism; however, all other recent large-scale prospective studies have failed to demonstrate a benefit in terms of prevention of, or outcome from, ARDS [53].

Several new therapies aimed at reducing white cell chemotaxis/activation or altering the balance of inflammatory mediators are currently under investigation. These agents include non-steroidal anti-inflammatory agents, vasodilatory prostaglandins, PGE/PGI immunotherapy [54], and phentoxifylline. All these agents have been shown to influence specific aspects of this syndrome, but large-scale studies of outcome are keenly awaited.

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