Acute Respiratory Distress Syndrome

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HISTORICAL PERSPECTIVES

Although Osler [1], as early as 1925, noted that sepsis resulted in a clinical condition that we all now recognize as acute respiratory distress syndrome (ARDS)\(^a\), it was not until 1967 that Ashbaugh and his colleagues [2] described the first series of these patients depicting a clinical illness characterized by dyspnea, tachypnea, diffuse pulmonary infiltrates and profound hypoxemia poorly responsive to oxygen therapy. Pathologic examination in seven of the original 12 patients showed pulmonary edema, the formation of hyaline membranes and atelectasis.

Because of its association with shock and trauma, particularly with its increasing incidence in the Vietnam War, it was referred to as “shock lung,” “Da Nang lung” and “traumatic wet lung.” Petty [3] called this condition the “adult respiratory distress syndrome” which remains its most popular moniker, but because this syndrome is also seen in children associated with similar etiologies, a consensus conference recently recommended the term “acute respiratory distress syndrome” [4]. In recognition that a spectrum of lung injury exists, this committee also recommended that the term “acute lung injury” (ALI) be adopted and that the term “ARDS” be reserved for the most severe form of ALI (ALI) (Tables 1 and 2).

ETIOLOGY

ARDS is the pulmonary manifestation of many pathophysiologic conditions. Most commonly, it occurs in the setting of direct lung injury such as aspiration of gastric contents, pneumonitis, pulmonary contusion and near drowning, or secondary to systemic inflammatory processes such as sepsis, pancreatitis, shock, trauma, etc. Indeed, even patient care therapies such as oxygen therapy and mechanical ventilation may result in the development or exacerbation of this pulmonary syndrome.

PATHOPHYSIOLOGY

ARDS develops secondary to the activation of both cellular and humoral inflammatory mechanisms. Activation of these mechanisms results in a process termed the “systemic inflammatory syndrome” (SIRS) [5], which is poorly understood, but has broad clinical

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\(^b\) Abbreviations: ARDS, acute respiratory distress syndrome; ALI, acute lung injury; SIRS, systemic inflammatory syndrome; MODS, multiple organ dysfunction syndrome; DVT, deep venous thrombosis; PEEP, positive end-expiratory pressure; CT, computerized tomography; PCOP, pulmonary capillary occlusion pressure; ECMO, extracorporeal membrane oxygenation; ECCO\(_2\)R, extra corporeal carbon dioxide removal; IVOX, intravascular oxygenation.
implications with the potential to effect cardiac, hepatic, renal, pulmonary and neurologic function. When multiple systems are simultaneously impacted, the process is referred to as “multiple organ dysfunction syndrome” (MODS) [5]. Of all the organs and systems affected by this inflammatory response, the lung seems to be the most vulnerable.

The basic science of SIRS and ALI is just beginning to be elucidated. Multiple cell types, cytokines and other mediators are now known to be involved including neutrophils, macrophages, lymphocytes, the vascular endothelium complement, interleukins, kinins, eicosanoids and elements of the coagulation cascade [6-9]. When SIRS affects the lung, abnormalities of surfactant (decreased production, inactivation [10]) occur, which further exacerbates pulmonary dysfunction.

Pathologically, ARDS has generally two distinct phases that overlap to some extent. An exudative phase occurs in the first several days (<7 days) and is characterized by alveolar capillary damage with resultant loss of water and protein into the alveolar spaces. Shortly thereafter, one begins to see hyaline membrane formation. Both processes contribute to the development of severe gas exchange abnormalities. A proliferative stage follows after about a week and is characterized by interstitial inflammation and the development of fibrosis.

Ventilator therapy itself can produce and/or exacerbate these pathophysiologic changes. It is generally recognized that oxygen concentrations greater than 50 to 60 percent may result in the release of leukotrienes, lipid peroxidation and neutrophil aggregation—all of which damage the lung [11, 12]. In addition, data accumulated over the last few years have led to the term “volutrauma.” It has been shown that alveolar over-distention from large tidal volumes, and independent of high airway pressures, results in mechanical changes that induce or worsen lung damage [13, 14]. Integrating this with Gattinoni’s data [15, 16], suggesting areas of lung with relatively normal compliance in ARDS, has recently led to alterations in the approach to mechanical ventilation in ARDS to limit the possibility of over-distention.

Table 1. Acute lung injury (ALI) [4].

| Description |
|-------------|
| Bilateral pulmonary infiltrates on chest x-ray |
| Pulmonary capillary wedge pressure ≤18 mmHg or no clinical evidence suggestive of increased left atrial pressure* |
| PaO₂ / FiO₂ ≤300** |

* It is possible to have both ARDS and elevated left atrial pressure coexist.
** Irrespective of positive end-expiratory pressure.

Table 2. Acute respiratory distress syndrome [4].

| Description |
|-------------|
| Bilateral pulmonary infiltrates on chest x-ray |
| Pulmonary capillary wedge pressure ≤18 mmHg or no clinical evidence suggestive of increased left atrial pressure* |
| PaO₂ / FiO₂ ≤200** |

* It is possible to have both ARDS and elevated left atrial pressure coexist.
** Irrespective of positive end-expiratory pressure.
PREVENTION OF ARDS

There are no known preventative therapies. Certainly, however, by attenuating or eliminating those etiologic processes that result in ARDS, we may be able to decrease its incidence.

Occasionally gastric aspiration is an inciting event for the development of ARDS. Lung injury is related to both the volume and pH of the aspirated material [17]. About 10 percent of all patients who clinically aspirate will go on to develop ARDS. When managing those critically ill patients at risk for gastric aspiration, steps should be taken to increase gastric pH (H₂ blockers and/or nonparticulate antacids), decrease gastric volume (nasogastric tube suction or prokinetic drugs when indicated) and ensure airway protection (cricoid pressure during intubation).

Fluid management may also impact the development and coarse of ARDS. Bickell [18] has shown that early and aggressive fluid resuscitation in patients with penetrating trauma prior to hospital evaluation contributed to the development of ALI. Additionally, patients who are over-hydrated have increased morbidity and mortality [19].

The incidence of ARDS should be decreased by: 1) ensuring deep venous thrombosis (DVT) prophylaxis, thereby decreasing pulmonary embolus; 2) elimination of infection-prone central lines when no longer indicated and decreasing the incidence of line sepsis; 3) utilizing appropriate pulmonary hygiene and decreasing the incidence of pneumonia; 4) feeding enterally when possible with subsequent decrease in bacterial translocation and sepsis; and 5) strict adherence to aseptic technique and avoidance of infection. However, no matter how attentive we are to these details of patient care, ARDS will continue to be seen and will demand our expertise in terms of clinical management and our commitment to continued investigation into its pathophysiology and potential therapies.

PROGNOSIS

Mortality from ARDS has decreased over the last several years to about 40 to 60 percent [20]. This progress is a result of the improvement in supportive care that we now provide. Pulmonary function in those patients surviving ARDS is remarkably maintained with the vast majority having normal or near normal pulmonary tests one year later. Indeed, it is a very small minority who have severe impairment of pulmonary function. These facts justify aggressive therapy with appropriate optimism in patients with ARDS, optimism that did not exist just a few years ago.

CURRENT MANAGEMENT OF ARDS

Supportive mechanical ventilation remains the centerpiece of care for patients with ARDS (Table 3). It must be emphasized, however, that careful attention needs to be directed towards other less glamorous aspects of care such as adequate intravascular volume and

Table 3. Current Management Thought in ARDS.

- Lung protection ventilator strategies
- Positive end-expiratory pressure
- Permissive hypercapnia
- Position changes
- Early diuresis
- Late corticosteroids
hemoglobin levels, nutrition and associated metabolic factors, DVT prophylaxis, stress ulcer prophylaxis, avoidance of nosocomial infection and a number of other patient care details.

ARDS results in many adverse pulmonary abnormalities including an increase in airway resistance, a decrease in functional residual capacity and compliance. Thanks to work byGattinoni and others, we now recognize that ARDS is not an evenly distributed pulmonary process [15, 16]. There exists a spectrum of pulmonary compliance changes with marked regional differences that result in a “smaller” “normal” lung. Traditional ventilation with large tidal volumes and high peak airway pressures in patients with ARDS can result in direct lung injury in those areas of lung with normal or relatively normal compliance by preferential delivery of volume to those areas and subsequent alveolar over-distention. It is this over-distention (not high pressure) that appears to injure and exacerbate lung damage.

This is the basis for recent recommendations regarding mechanical ventilation. The use of lower tidal volumes (5 to 8 mL/kg) to avoid peak pressures (>35 cm H2O), the use of decelerating waveform for gas delivery, the restriction of FiO2 to maintain acceptable oxygen saturations (88 to >90 percent) for a given individual, and positive end-expiratory pressure (PEEP) are mechanical ventilator parameters that are now advocated.

PEEP has been shown to improve oxygenation, increase lung volumes, decrease shunt fraction and improve pulmonary compliance by a variety of mechanisms including redistribution of lung water, increased alveolar volume, recruitment of previously collapsed alveoli, reducing the opening and closing of alveoli with tidal ventilation subsequently decreasing shear forces and potentially inhibiting further damage [21-23].

Obviously, PEEP has disadvantages in terms of barotrauma, cardiovascular stability and potential increases in dead space. This has led to a large number of differing ventilatory approaches that have led to “optimal” PEEP, “best” PEEP, “preferred” PEEP, “least” PEEP and PEEP titrated to minimize dead space. In the absence of compelling evidence supporting any particular PEEP strategy, it seems prudent to follow a “least” PEEP therapy, which uses the lowest PEEP necessary to maintain acceptable oxygenation with an FiO2 less than 0.6. With such an approach, there appears to be less interference with hemodynamics requiring less intravascular volume and inotropic support and a lesser incidence of pneumothorax.

Permissive hypercapnia

A common adjuvant to the above ventilator strategy is “permissive hypercapnia,” allowing carbon dioxide to rise (pH ≥7.2). Described by Hickling [25], there has been improved survival associated with its use [25-27]. It allows the use of smaller tidal volumes, limited peak pressures and lower rates inherent in lung protection strategies. It is generally well tolerated if implemented slowly. There are a few patients in whom it cannot be employed (increased intracranial pressure, ongoing metabolic acidosis, etc.), and in our experience, it is reasonable therapy.

Pressure-controlled ventilation

Ironically, ventilators became volume cycled to ensure a given tidal volume in patients with poor compliance. We now know that the high pressures that are generated in this mode in patients with low compliance contributes to, or perhaps even causes, direct lung damage. This has resulted in a return to pressure-control methods of ventilation using ventilators that at are time cycled and triggered. The advantage of these methods is an ability to maintain but not exceed preset inspiratory pressures. The disadvantages are a varying flow rate, and depending upon changes in pulmonary compliance, a potentially varying tidal volume. There is some evidence that there are alveoli recruited by pressure ventila-
tion that are not recruited when using conventional volume-control methods. Constant inspiratory pressure, along with PEEP, allows one to arrive at a higher mean airway pressure (the driver for oxygen) at lower peak airway pressures.

These characteristics allow management in such a way as to avoid volutrauma and barotrauma with greater assurance. It also introduces some additional potential for operator error, particularly when coupled with inverse I:E ratios, since the result of increases in rate (or decreases in compliance) may actually decrease tidal volume ventilation.

**Inverse ratio ventilation**

The use of inverse ratio ventilation is increasing in adults following its successful use in newborns. The use of inspiratory times that are equal to or greater than expiration (normal ratio is 1:2) is said to result in greater alveolar recruitment, leading to alveolar stabilization of the lung by not allowing them to collapse below closing volume. Other reported benefits are the ability to decrease peak inspiratory pressures, levels of PEEP, mean airway pressure and minute ventilation [28, 29]. There is no compelling evidence, however, that this is the case. Most data suggest that the creation of intrinsic or auto-PEEP with short expiratory times is responsible for these changes.

Nearly all patients with ARDS being mechanically ventilated will require sedation and occasionally neuromuscular paralysis. The provision of analgesia and anxiolysis are appropriate components of compassionate care. The use of neuromuscular blocking agents remains more controversial, but they can have benefit. Paralysis may decrease oxygen consumption and carbon dioxide production in certain situations. Marked tachypnea that occurs in these patients has been shown to detract from the beneficial effects of PEEP and may need to be controlled by paralysis [30]. Lastly, because of the need to control rate in patients receiving pressure-controlled inverse ratio ventilation (because increasing rate will decrease expiratory time, decreasing tidal volumes, and potentially producing dangerous levels of intrinsic PEEP), sedation and paralysis are required.

![Figure 1. Left: Computerized tomographic scan of a lung in a patient with ARDS demonstrating normal areas of the lung and areas with interstitial/alveolar infiltrates. Right: Chest x-ray of the same patient demonstrating diffuse pulmonary edema.](image)
Position changes

Patient position changes may represent another useful adjunct for improving gas exchange in ARDS. When one examines computerized tomographic (CT) scans of patients with ARDS, the nonhomogenous nature is readily apparent, with the majority of disease in dependent areas (Figure 1). Oxygenation can be improved in the prone position [31, 32], but turning critically ill patients with multiple tubes and catheters to the prone position is inherently dangerous. Additionally, no study has yet demonstrated improved outcome with the prone position.

Early diuresis

Intravascular fluid management can be complex in patients with ARDS, particularly in patients with trauma or sepsis. There is evidence that pulmonary gas exchange and outcomes are improved when patients undergo diuresis and fluid restriction with decreasing pulmonary capillary occlusion pressure (PCOP) and body weight [33-35]. This must be balanced against potential hypovolemic states that compromise renal or other organ perfusion.

EXPERIMENTAL MANAGEMENT OPTIONS IN ARDS

Mortality remains high in ARDS, and the search continues at a rapid pace to find other ventilator-related and more specific therapies for patients with ARDS (Tables 4 and 5).

Steroids

Two prospective studies have discredited the use of steroids in the early acute care of patients with ARDS [36, 37]. Recent data have suggested a role for steroids in the proliferative phase of ARDS characterized by fibrosis [38].

Surfactant replacement

As surfactant significantly alters function in ARDS, high hopes existed that provision of this important element exogenously would be beneficial. Unfortunately, this has not

Table 4. Experimental therapies.

- Steroids
- Surfactant replacement
- Nitric oxide
- Partial liquid ventilation
- Ketaconazole
- Antioxidant therapy
- Nutritional alterations
- High-frequency ventilation
- Antibody therapy

Table 5. Extrapulmonary technology.

- Extracorporeal membrane oxygenation (ECMO)
- Extracorporeal carbon dioxide removal (ECCO2R)
- Intravascular oxygenation (IVOX)
been proven in ARDS. It is an expensive therapy, one for which there is thus far no evidence of outcome benefit in sepsis-related ARDS [39].

Nitric oxide

Nitric oxide was found in 1987 to be endothelial-derived relaxing factor [40] and subsequently shown to act as a selective pulmonary vasodilator when inhaled [41, 42]. It has no systemic side effects because of its short half-life. Since it is delivered only to ventilated lung regions, it was suggested that this was a pulmonary vasodilator that would not increase shunt and, therefore, would be advantageous in ARDS by decreasing pulmonary artery pressure and enhancing ventilation perfusion matching. Uncontrolled studies confirm decreases in pulmonary hypertension and some decrease in pulmonary shunt fraction and improvement in gas exchange [43, 44].

Despite the enthusiasm following the initial studies, it remains to be seen whether nitric oxide improves outcome in patients with ARDS or subgroups of patients with ARDS.

Total/partial liquid ventilation

Perflubron is a perfluorocarbon that is an inert, colorless liquid. It is an efficient oxygen carrier, has low surface tension and has been reported to have a positive impact on local inflammatory processes [45, 46]. Clinically, perflubron has been shown to increase compliance (allowing for lower airway pressures) and improve oxygenation when instilled into the lung to functional residual capacity and the patient ventilated with conventional techniques. It is thought to recruit atelectatic lung, redistribute pulmonary blood flow, stimulate surfactant production and displace alveolar debris and edema [46, 47]. Experience in adults, however, has been disappointing, and the Food and Drug Administration recently stopped a pediatric trial. The future of this technique is unknown.

Ketoconazole

Ketoconazole is an agent that modulates eicosanoid activity, specifically thromboxane and, as such, is of potential benefit in ARDS. Although initial results seem encouraging [48], the National Institutes of Health's ARDS network was unable to confirm benefit to ketoconazole.

Antioxidant therapy

The production of free radicals of oxygen is thought to be a major factor in the pathophysiology of this process. Animal studies have demonstrated some benefit [49, 50], but clinical human trials remain inadequate.

Nutritional alterations

Though preliminary, there is evidence that manipulation of mediator formation by dietary formulas containing high amounts of select fatty acids and antioxidants improves oxygenation, airway pressure and outcome in animals and humans with ARDS [51, 52].

High-frequency ventilation

High-frequency ventilation was initially described in 1972. Its use of small tidal volumes (1.3 mL/kg) and high rates (300-2400 breaths/min) makes it unique in terms of gas transport. In the pediatric population, high frequency ventilation has been shown to improve survival and cause less barotrauma than conventional techniques [53]. In adults, studies have been mixed with the general consensus that there is no significant advantage over conventional techniques [54]. Its use continues in adults, usually when all other efforts to adequately oxygenate the patient have failed.
Antibody therapy

It has been anticipated that the development of antibodies directed against the major elements of SIRS (tumor necrosis factor, endotoxin, interleukin, etc.) or receptor antagonists would result in improved outcome in the disease states characterized by this response (sepsis, ARDS, MODS) [55, 56]. Thus far, this approach has proven expensive and ineffective. It is likely that the complexity of the inflammatory response is such that there is not a single "magic bullet" inhibitor that can be used to treat ARDS.

Extrapulmonary technologies

These techniques have been developed to provide respiratory support as a bridge until resolution of the patient's ARDS begins to occur, and additionally to "protect" the lungs from the detrimental effects of more conventional therapies such as oxygen toxicity and volutrauma. Unfortunately, these techniques are expensive, require additional skilled personnel and have inherent danger in their use.

Extracorporeal membrane oxygenation (ECMO)

In the 1970s, extracorporeal membrane oxygenation (ECMO) failed to demonstrate a change in outcome in adults with ARDS [57]. Despite this, there is ongoing interest in this technique, and a few centers continue to use it primarily as a salvage technique when all other efforts fail [58].

Extracorporeal carbon dioxide removal (ECCO₂R)

Gattinoni and colleagues used this technique as a means of providing carbon dioxide removal by venovenous bypass [59]. This allowed lower respiratory rates and volumes with subsequent decreased airway pressure—in short "resting the lungs." Morris [60] and his group, in a prospective study, could show no additional benefit compared to more conventional therapy using ECCO₂ for patients with ARDS.

Intravascular oxygenation (IVOX)

The IVOX is an intravascular oxygenating device that consists of multiple filaments through which oxygen flows under negative pressure. This device had limited gas exchange (30 to 40 percent of total) and required anticoagulation [61]. No device currently exists for clinical use.

CONCLUSION

ARDS is a systemic disease manifested in the lung. Its etiologies are multiple and varied. At the present time, no specific therapy exists, and care is largely supportive through the use of mechanical ventilation, avoidance of complications and therapy directed towards the initiating problem. Thus far, we have become better at supportive care, allowing the mortality from ARDS to decrease to as low as 40-60 percent. Most experts feel this is the limit of improvement that we can expect from improving our approach to supportive care (avoiding volutrauma, barotrauma, oxygen toxicity and other complications). Thus, the search continues for more specific therapy and newer interventions such as partial liquid ventilation, control of the inflammatory response, nitric oxide, and temporary pulmonary replacement therapy (IVOX, ECMO, ECCO₂R).

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