The Acute Respiratory Distress Syndrome: Myths and Controversies

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Abstract

The term Adult Respiratory Distress Syndrome (ARDS), was first introduced by Ashbaugh and Petty more than two decades ago. Since then, our understanding of this clinicopathological entity has increased significantly. However, little therapeutic progress has been achieved and the mortality remains high. ARDS is characterized by diffuse pulmonary microvascular injury resulting in increased permeability and, thus, non-cardiogenic pulmonary edema. Ventilation-perfusion lung studies have demonstrated that the predominant pathogenesis of hypoxemia in ARDS is related to intrapulmonary shunts. Common symptoms include dyspnea, tachypnea, dry cough, retrosternal discomfort, and moderate to severe respiratory distress. In most cases the diagnosis of ARDS is that of exclusion. The mainstay of therapy for this syndrome is the management of the underlying disorder causing it. To date, there are no specific pharmacological interventions of proven value for the treatment of ARDS. Once the potentially treatable sources have been found and their therapy started, the main treatment for ARDS is supportive.

Ashbaugh and coworkers, in 1967, described a syndrome characterized by refractory hypoxemia, diffuse lung infiltrates on chest radiograph, and decreased lung compliance in a group of 12 patients suffering from severe respiratory failure.[1] In addition, these patients had different underlying diseases (e.g. pancreatitis, pneumonia, trauma). Originally, this condition was named by the authors as the Acute Respiratory Distress Syndrome of Adults. However, in 1971 the same authors renamed the syndrome to what we now know as the Adult Respiratory Distress Syndrome or Acute Respiratory Distress Syndrome (ARDS).[2] Since then, our understanding of this clinicopathological syndrome has increased significantly. Although the vast majority of patients with ARDS are ultimately managed in intensive care units (ICU), the purpose of this article is to present to emergency physicians, intensivists, surgeons, and other health care providers a review of the pathophysiology, early clinical features, diagnosis, acute management and prognosis as well as some of the common myths and controversies of this devastating syndrome.

DEFINITION

The definition of ARDS has changed over time. In the early 1960s Burke and coworkers utilized the term High Output Respiratory Failure to describe a type of respiratory failure characterized by the inability to provide adequate oxygenation and carbon dioxide excretion.[3]

Terms frequently used when referring to this syndrome include: adult hyaline-membrane disease, adult respiratory insufficiency syndrome, congestive atelectasis, hemorrhagic lung syndrome, Da Nang lung, stiff-lung syndrome, shock lung, white lung and, wet lung among others.[4]

Although there are currently diverse opinions regarding the proper use of the term “ARDS”, all definitions of this syndrome include patients who meet the following criteria:[5,6]

1. Clinical evidence of respiratory distress.
2. Chest radiograph revealing diffuse bilateral airspace disease (“pulmonary edema”).
3. Hypoxemia that is difficult to correct with oxygen supplementation.
4. Hemodynamic evidence of a pulmonary artery occlusion (wedge) pressure < 18 mm Hg.
5. Thoracic static compliance less than 40 mL/cm of water.

INCIDENCE

The incidence of ARDS varies depending on the diagnostic criteria used for its definition, as well as the underlying diseases that are acting as risk factors. The estimated incidence of ARDS in the USA in recent years has been calculated to be close to 150,000 new cases each year.[7,8] In a study by Fowler and coworkers, the incidence varied from 2% (e.g. in patients post coronary-artery bypass grafts or burns) to 36% (e.g. gastric bronchoaspiration).[9] In a similar cohort, Pepe et. al., found that the incidence of ARDS ranged from 8% (in patients with multiple fractures) to 38% (in patients with sepsis).[10]

ETIOLOGY

The major risk factors for the development of ARDS are depicted in Table 1. Among them, the most frequently seen in clinical practice are sepsis, bronchial aspiration of gastric contents, multiple trauma, massive blood transfusions and low-perfusion states.9, 10, [11]

- Aspiration of gastric contents
- Burns
- Cardiopulmonary bypass
- Disseminated intravascular coagulation
- Drugs
- Multiple fractures
- Multiple transfusions
- Near-drowning
- Pancreatitis
- Prolonged hypotension
- Sepsis
- Toxin inhalation
- Trauma

Table 1. Common causes of ARDS

PATHOPHYSIOLOGY

The basic abnormality in ARDS is the disruption of the normal alveolar-capillary barrier. Moreover, it is now evident that ARDS is not simply a form of pulmonary edema caused by increased microvascular permeability, but only a manifestation of a more generalized permeability defect.[12]

Research in recent years has been focused on possible mediators of lung injury in ARDS such as free radicals, proteinases and, soluble agents including cytokines, arachidonic acid metabolites and charged proteins.5

The pathophysiologic consequences of lung edema in ARDS include a decrease in lung volumes, compliance, and large intrapulmonary shunts (blood perfusing unventilated segments of the lung). A fall in the residual volume is uniformly present and contributes to ventilation/perfusion inequality.[13]

It has been hypothesized that a defective surfactant may be partially responsible for the small lung volumes and that it may worsen edema accumulation in ARDS (as increases in alveolar surface tension have been shown to increase lung water content by lowering interstitial hydrostatic pressure).[14,15] The decrease in lung compliance is secondary to the increased lung recoil pressure of the edematous lung, which clinically increases the work of breathing and leads to respiratory muscle fatigue.15

The pulmonary vasculature is prominently affected in ARDS. Pulmonary hypertension not related to hypoxemia is a very common finding in patients with ARDS. Indeed, this is caused by a three-to-five fold increase in the pulmonary vascular resistance (PVR) and is associated with an increase in the right ventricular work.[16] The reversibility of the early pulmonary hypertension (within 72 hours of syndrome onset) by administration of nitroprusside or isoproterenol suggests that vasoactive inflammatory mediators are involved, and the fixed nature of the late pulmonary hypertension is probably due to in situ thrombosis and fibrosis occluding the vascular beds. Pulmonary angiography studies performed within 48 hours of the onset of ARDS have shown that 48% of patients have demonstrable filling defects (intravascular thrombi) in vessels of more than 1 mm of diameter.[17]

Patients who die of respiratory failure usually show a progressive decrease in lung compliance, worsening hypoxemia and, progressive increase in dead space with hypercapnia. Pathological examination of the lungs in these patients reveals extensive interstitial and alveolar fibrosis.[18]

CLINICAL MANIFESTATIONS

The signs and symptoms of ARDS may develop either insidiously or over the period of hours or days after the initiating event (e.g.sepsis). On occasion the development of ARDS coincides with the predisposing illness (e.g. gastric

content aspiration). Common symptoms include dyspnea, tachypnea, dry cough, retrosternal discomfort, and agitation. The patient appears in moderate to severe respiratory distress and may have cyanosis. Examination of the lungs may reveal coarse crackles and bronchial breath sounds.[19] This clinical picture usually deteriorates, and the patient eventually requires assisted mechanical ventilation.

When the patient is in the appropriate hospital setting, hemodynamic parameters (using a balloon-tipped, flow-directed or Swan-Ganz catheter), reveal a normal or near-normal pulmonary artery occlusion (wedge) pressure.5 This provides important information, since elevated left ventricular filling pressures are the hallmark of cardiogenic pulmonary edema. On the other hand, low or normal pressures provide convincing evidence that the edema is due to increased permeability (provided that therapy with diuretics has not been instituted). If the patient has previously received diuretic therapy, the pulmonary artery occlusion pressure may be falsely low. Central venous pressure measurements do not provide similar information because the right and left ventricles often differ considerably in their performance and filling pressures.[20]

Barotrauma (e.g. pneumothorax, pneumomediastinum, subcutaneous emphysema) is a frequent complication in patients with ARDS managed with mechanical ventilation. Patients at high risk for barotrauma, are those with very low lung compliance (e.g.< 20 cm of water). Development of barotrauma is most closely associated with alveolar distension, which best correlates with high peak inspiratory pressures.[21]

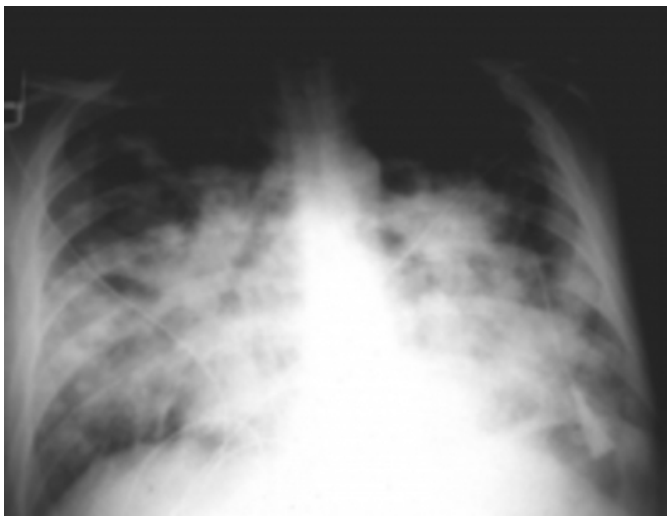
DIAGNOSIS

Due to the fact that there are no sensitive nor specific markers of pulmonary endothelial/epithelial injury, the diagnosis of ARDS is presently made by physiologic criteria that are themselves controversial.6 As mentioned earlier, the diagnosis of ARDS is that of exclusion. Nevertheless, some laboratory and radiographic tests may be useful.

Arterial blood gases usually reveal severe hypoxemia (e.g. PaO2 50 mm Hg), and in many instances, hypocapnia. Hypoxemia in patients with ARDS is difficult to correct with the use of supplemental oxygen.5

Figure 1

Figure 1. The chest roentgenogram typically shows diffuse bilateral infiltrates.



Diffuse pulmonary consolidations with air bronchograms are the result of ARDS following smoke inhalation. The appearance is radiologically very difficult to distinguish from alveolar edema or diffuse pneumonia.

In most instances it is difficult to differentiate radiographically between cardiogenic and non-cardiogenic pulmonary edema (or ARDS).19 However, there are certain radiographic signs and patterns that can be helpful in making this differentiation, including:[22]

1. In ARDS the cardiovascular silhouette size is usually normal.
2. Patients with ARDS have a more peripheral, uneven and patchy distribution of pulmonary edema when compared with the even and perihilar (bat-wing) features of cardiogenic pulmonary edema.
3. The incidence of pleural effusions in ARDS is less than that of cardiogenic pulmonary edema.

Some radiologists consider that the width of the vascular pedicle is usually larger in cardiogenic pulmonary edema than in ARDS.[23] However, in our experience these findings are not sensitive nor specific.

TREATMENT

To date, there are no specific pharmacological interventions of proven value for the treatment of ARDS. Although corticosteroids and prostaglandin E1 have been widely used

clinically, recent studies have failed to show any benefit in outcome, lung compliance, pulmonary shunts, chest radiograph, severity score or survival.[24, 25, 26, 27]

The mainstay therapy of ARDS is the management of the underlying disorder causing it, when feasible. Unfortunately, this is not always possible (as is the case of aspiration of gastric contents,smoke inhalation or trauma). Treatable causes of ARDS include sepsis, respiratory infections and shock.

Once in the ICU, a pulmonary artery (PA) catheter should routinely be placed in patients with suspected ARDS. Although in prospective studies the presence of a PA catheter has not modified outcome,[28] in our experience the PA catheter will serve as a diagnostic tool to assess vascular filling pressures allowing management of oxygen and positive end-expiratory pressure (PEEP) levels by providing calculations of oxygen delivery, and the information necessary for an appropriate fluid management.26

As with any patient with a critical illness, maintaining an airway, adequate oxygenation and support of the circulation are essential in the management of patients with ARDS. The goals of supportive therapy in ARDS include:

(1)Ventilatory support: Assisted mechanical ventilation should be instituted in any patient with ARDS in respiratory failure or impending respiratory failure. We must stress the importance of early assisted ventilation, as prolonged failure to meet the oxygen needs of the tissues will eventually lead to cellular death and organ dysfunction. Once the patient is intubated, the ventilator should be placed on assist-control or intermittent mandatory ventilation, fractional concentration of inspired oxygen (FiO2) of 1 and a tidal volume of 8-12 cc/Kg of ideal body weight. The FiO2 should be reduced as soon as possible. The use of alternate modes of ventilation (i.e. High frequency jet ventilation, inverse ratio ventilation) have not been proven to improve survival.

PEEP is the most effective way to maintain adequate oxygenation in patients with ARDS.[29,30] It improves oxygenation by increasing the functional residual capacity (FRC) and recruitment of alveoli. However, PEEP may have deleterious effects on cardiac output by decreasing venous return. Indeed, the optimal level of PEEP is still controversial. In general, PEEP should be titrated gradually with serial calculations of cardiac output and oxygen delivery, allowing less FiO2 (and thus, less oxygen toxicity). When patients with ARDS are placed on mechanical ventilators for support, PEEP should be started when a FiO2 over .5 is required to maintain a PaO2 > 55 mm Hg; the initial level of PEEP should be between 3 and 5 cm of water and increased by 2 cm of water until either a PaO2 > 55 mm Hg is obtained with a FiO2 .5 or a decrease in oxygen delivery occurs. Once started, PEEP should not be abruptly discontinued, as a severe fall in PaO2 may occur.29 Despite the fact that the use of PEEP will improve oxygenation and oxygen delivery, there is no scientific evidence that PEEP improves neither lung injury nor survival.[31,32]

(2) Prevention, diagnosis and therapy of infections and superinfections

(3) Minimizing the accumulation of pulmonary edema fluid without compromising renal function.

(4) Adequate nutritional support.

A number of new management approaches are being explored in ARDS. Monoclonal antibodies against common determinant of bacterial lipopolysaccharide have shown controversial results in preventing the development of ARDS in patients with sepsis. Other therapies currently under investigation include: pentoxifylline, inhibition of tumor-necrosis-factor (TNF) and phosphodiesterase inhibitors.34-36 Of particular interest is the use of surfactant in ARDS. As mentioned earlier, surfactant deficiency is a crucial component of this syndrome.14,24 Although the data are spare, humans with ARDS appear to have either abnormal quantities of surfactant, abnormal composition of surfactant or both. Preliminary data using this form of therapy in patients with ARDS is encouraging.[33]

PROGNOSIS

The mortality of ARDS on different studies has remained between 50% and 70%. No statistical difference has been demonstrated in outcome since 1971 in spite of medical technological advance.5,9,11 It is, therefore, inferred that better supportive care has had no impact on survival.11

The mortality of patients with ARDS is mainly related to multiple organ failure rather than pulmonary dysfunction. In a study by Montgomery et.al., less than 20% mortality in ARDS was due to irreversible respiratory failure.37

Patients who survive ARDS manifest surprisingly minimal long-term impairment of lung function.38,39 These patients may have mild restrictive impairment and gas-exchange deficit, and occasionally can exhibit partially reversible airway obstruction.38,40 Long term abnormalities are more

likely to occur in patients treated for prolonged periods of time with oxygen supplementation greater than 0.5.41-46

CONCLUSIONS

In ARDS, direct toxins, free radicals, charged particles and cytokines, all work on specific components of the alveolar capillary cells to result in altered permeability. Clearly, much more work will be needed to unravel the details of the cellular mechanism of normal and altered permeability. This new knowledge will lead to new early diagnostic and therapeutic approaches that may be started in the emergency department, hospital ward or ICU upon patient's presentation, perhaps leading to a decline in ARDS mortality.

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