Specialty Conference

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Adult Respiratory Distress Syndrome

Many causes for the adult respiratory distress syndrome (ARDS) have been reported, all with common pathologic, pathophysiologic and biochemical end results. The final common pathway may involve changes in lung content of a critical enzyme, superoxide dismutase, or alterations in surfactant metabolism, or both. The early assumption that the disorder is partially due to oxygen toxicity from inspired oxygen concentrations greater than 60 percent is consistent with findings of recent biochemical studies. Although the lung normally maintains its alveoli dry, during ARDS increased permeability of small pulmonary vessels results in primary pulmonary edema, in contrast to edema from increased vascular pressure. These data have been obtained mainly in animals; whether they apply to humans with ARDS is not certain. Tissue oxygenation is improved by increasing end-expiratory pressure in an animal model of ARDS, more effectively during spontaneous breathing than during mechanical ventilation. During spontaneous breathing, adverse ventilatory effects were caused by stimulation of pulmonary reflexes.

DANIEL H. SIMMONS, MD, PHD:* *As there are several excellent reviews of the adult respiratory distress syndrome* (ARDS), *the most recent by Hopewell and Murray,[1] and by Petty and Newman,[2] this symposium will focus on specific areas of current interest in which significant developments are occurring.*

The adult respiratory distress syndrome was first named by Ashbaugh and associates[3] in 1967. In 1971 it was described more completely by

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
CPAP = continuous positive airway pressure
DAD = diffuse alveolar damage
FIO_2 = fractional concentration of inspired oxygen
$PaCO_2$ = arterial carbon dioxide partial pressure
PaO_2 = arterial oxygen partial pressure
PEEP = positive end-expiratory pressure
PO_2 = oxygen partial pressure
PS = permeability surface area products
PvO_2 = mixed venous blood oxygen partial pressure
TLC = total lung capacity

Petty and Ashbaugh[4] when they characterized the syndrome by specific clinical, physiologic, radiologic and pathologic criteria, correlating earlier reports from these fields of interest. Their criteria included the following:

- Clinical—*respiratory distress, tachypnea and cyanosis.*
- Physiologic—*refractory hypoxemia (now known to be caused by increased intrapulmonary shunting) and high inflation pressure during mechanical ventilation (or low lung compliance, the "stiff lung" syndrome).*
- Radiologic—*diffuse alveolar infiltrates.*
- Pathologic *(based on early autopy findings)* —*pulmonary congestion, hyperemia and formation of hyaline membranes.*

There have been many synonyms for ARDS, *both before and after these descriptions. These include shock lung, traumatic wet lung, adult hyaline membrane disease, acute respiratory failure, postperfusion lung, oxygen toxicity lung, wet lung, Da Nang lung, diffuse alveolar injury, acute diffuse lung injury and noncardiogenic pulmonary edema. Two other names—primary pulmonary edema and diffuse alveolar damage* (DAD)—*will be suggested by participants in this conference. This multitude of synonyms reflects early confusion about the syndrome because the names used were based on various factors: specific causes (such as oxygen toxicity of lung), appearance of the lung (traumatic wet lung), the situation in which the syndrome arose (shock lung), the clinical features (adult hyaline membrane disease), laboratory data (acute respiratory failure) or on pathophysiologic studies (noncardiogenic pulmonary edema). Two of the recent synonyms most commonly used are diffuse alveolar injury and noncardiogenic pulmonary edema, both of which carry implications about the cause and pathophysiology of the disorder.*

TABLE 1.—*Disorders Associated with Adult Respiratory Distress Syndrome**

Shock of any etiology	*Inhaled toxins*
Infectious causes	Oxygen
Gram-negative sepsis	Smoke
Viral pneumonia	Corrosive chemicals (nitrogen dioxide, chlorine, ammonia, phosgene, cadmium)
Pneumocystis carinii	
Cytomegalovirus	*Hematologic disorders*
Trauma	Intravascular coagulation
Fat emboli	Massive blood transfusion
Lung contusion	Postcardiopulmonary bypass
Nonthoracic trauma	*Metabolic disorders*
Head injury	Pancreatitis
Liquid aspiration	Uremia
Gastric juice	Paraquat ingestion
Fresh and salt water	*Miscellaneous*
Hydrocarbon fluids	Lymphangitic carcinomatosis
Drug overdose	Increased intracranial pressure
Heroin	Eclampsia
Methadone	Postcardioversion
Propoxyphene	Radiation pneumonitis
Barbiturates	

*Adapted from Hopewell and Murray.[1]

There has been much controversy about the use of the term adult respiratory distress syndrome, some authors advocating its use because it can act as a unifying concept for directing therapy,[5] others objecting because it may distract from consideration of specific causes, which are often critical in its management.[6]

Although ARDS *is caused by various physical disorders (Table 1), the pathologic and pathophysiologic results are strikingly similar. These consequences include diffuse injury to interalveolar septa, increased permeability of vascular endothelium and alveolar epithelium, intravascular platelet aggregation and many other abnormalities.[7-9] These disorders in turn lead to the classic physiologic, radiologic and pathologic findings. Table 1 is as important in pointing out the many associated disorders as it is in identifying each one. The extent of this list has little effect on whether the term adult respiratory distress syndrome should be used; it does indicate that attention to the cause may be critical.*

Adult respiratory distress syndrome occurs in about 150,000 persons each year, the estimated incidence in 1972.[10] This incidence may still be increasing;[1] however, it is not clear whether the reported increase is due to increased awareness of the disorder or to a true increase in incidence. The mortality due to this disorder is high, probably greater than 50 percent, but there are no exten-

sive data to confirm this. Frequency of diagnosis of milder cases is likely a major factor in determining the mortality. Although the mortality may be decreasing, the decrease is not significant,[1] *despite dramatic improvements in therapy of the disorder. This raises important questions about the true value of the therapeutic modalities developed in recent years and accepted as being valuable.*

Pathology of ARDS

GERALD NASH, MD*

IN THE MIDDLE 1960's when ARDS was emerging as a clinical entity, pathologists were impressed with unusual gross and microscopic appearances of the lungs of patients who had died as a result of the syndrome. In 1967 Drs. Nash, Blennerhassett and Pontoppidan[11] reported on an autopsy study of patients (many with ARDS) who had died in a respiratory intensive care unit. In that study, the lungs of those patients were compared with those of patients in a control autopsy population who had not had acute respiratory failure and who had never been treated with a mechanical ventilator. A wide range of gross and microscopic changes were encountered with approximately equal frequency in the two groups. However, two distinctive lesions were found in the study group that set this group apart from the control population.

The first lesion was characterized grossly by heavy consolidated lungs that had a homogeneous beefy-red appearance. Only a small amount of serosanguineous fluid could be scraped from the cut surface; the foamy pink fluid, characteristic of intraalveolar edema, was not present. Microscopically, such lungs showed capillary congestion, marked interstitial edema, a moderate amount of intraalveolar fibrinous exudate and focal alveolar hemorrhage. The most striking finding, and one which typified this lesion, was the presence of hyaline membranes lining alveolar ducts, alveoli and some respiratory bronchioles.

The second lesion, which separated the study group from the control population, was a pattern of early interstitial fibrosis found in many patients who had died in the respiratory unit. Viewed grossly, the lungs of these patients were characterized by a greyish-pink consolidation without demonstrable exudate, suggesting a degree of fibrous organization. On microscopic examination, there was pronounced interstitial thickening with a combination of edema fluid, histiocytes, fibroblasts, increased reticulin and collagen fibers. The normal alveolar surface had been replaced by large rounded or cuboidal cells, a finding commonly referred to as "hyperplasia of alveolar lining cells" by pathologists. Some lungs in the patients of the study group showed a combination of the two distinctive patterns, with evidence of hyaline membranes undergoing organization and early interstitial fibrosis.

When the pathologic changes were correlated with the duration of ARDS, it became apparent that the two distinctive lesions, which characterized the lungs of the patients in the study group, were really phases in the evolution of a particular type of morphologic response of the lung to injury. In general, patients with ARDS who died after a week or less had the interstitial edema-hyaline membrane pattern. Those who lived two weeks or more had the early interstitial fibrosis pattern, and patients who died after one to two weeks had a combination of the two patterns. The interstitial edema-hyaline membrane lesion was called the exudative phase and the early interstitial fibrosis picture was the proliferative phase of the process.

A closer look at the clinical information available on the study group patients showed that patients with the exudative or proliferative lesions had been treated with toxic concentrations of oxygen for prolonged periods. We concluded that the lesions probably represented phases in the evolution of pulmonary oxygen toxicity in man. Additional studies by other investigators on similar patients with ARDS showed comparable findings and also implicated oxygen toxicity as the likely cause of the lesions.[12-15] Furthermore, the findings in experimental studies showed that the exudative and proliferative lesions described in patients with ARDS could be reproduced in animals by exposing them to toxic concentrations of oxygen for prolonged periods.[16-19]

These studies led to a judicious use of oxygen in the treatment of acute respiratory failure, with an attempt to avoid administering toxic levels unless absolutely necessary to maintain life. In the new enlightened era of oxygen therapy, some patients died with complications of ARDS who had never required and therefore never received toxic concentrations of oxygen. When their lungs were

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