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ADULT RESPIRATORY DISTRESS SYNDROME

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INTRODUCTION

For more than a decade, the adult respiratory distress syndrome (ARDS) has stimulated the interest of clinicians, roentgenologists, physiologists, pathologists, experimental biologists and others in the clinical and basic sciences. The characterization of the syndrome and the development of a systematic, although emperic therapy have been among medicine's major advances. However, after a decade marked by progress in the refinement of intensive care techniques and in the understanding of alveolar-capillary permeability, it is clear that improved survival in ARDS is not likely attainable through the development of improved life support technology. Thus, the mechanisms by which insults lead to this lung injury have been an area of intense research. This presentation will first briefly summarize the history of this syndrome and review its clinical and pathological features. It will then concentrate on recent progress in the understanding of the pathophysiology of acute alveolar injury, the regulation of the pulmonary reparative response and the possibilities for therapeutic modification in the course of ARDS.

HISTORY

ARDS has been accepted as a distinct category of acute lung disease only within the last 15 years, but physicians have been aware of related disease processes for many years (1, 2). A syndrome of "massive collapse of the lungs" was described in 1914 in which "total deflation of a large area of lung tissue due to failure of inspiratory power" was noted (3). This syndrome was recognized in 0.8% of 1,930 postoperative patients over a two year period from 1911 to 1913. Acute respiratory failure was also identified in battlefield casualities in World War I (4). At that time most severely traumatized patients did not live long enough to develop respiratory insufficiency, and the few who were resuscitated after severe shock often died rapidly from what was then called "post-traumatic massive pulmonary collapse". Advances in medical facilities and improved therapy for shock resulted in a considerable number of World War II and Korean conflict casualities surviving only to develop a life threatening complication which become known by a variety of names including "traumatic wet lung" or "blast lung" (5). An autopsy study of casualities of World War II was the first to note a high incidence of atelectasis, hyperemia, and edema in the lungs of soldiers dying from shock secondary to severe trauma (6). In 1950, Jenkins, of this institution, used the term "congestive atelectasis" to describe similar findings in 7 civilian patients who died of respiratory failure associated with recent trauma, surgery, or sepsis (7). In 1960, patients dying of respiratory failure following open heart surgery in which a pump oxygenator was used were noted to have similar findings (8). During the war in Vietnam as more rapid methods of battlefield evacuation become available and problems of renal failure yielded to hemodialysis, physicians in the field encountered increasing numbers of military personnel who developed respiratory complications following thoracic and nonthoracic trauma. The term "DaNang Lung" was applied to this frequently fatal syndrome. In an autopsy study of 100 combat casualities who died after field resuscitation, 89% had histologic evidence of pulmonary edema, congestion and alveolar hemorrhage (9). Those surviving for more than 5 days had a high incidence of pneumonia and alveolar hyaline membranes.

In 1967, Ashbaugh, et al., described 12 patients with severe dyspnea, hyperemia unresponsive to oxygen therapy, decreased lung compliance, and diffuse alveolar infiltrates on chest x-rays (1). The syndrome was precipitated by a variety of insults including severe trauma, viral infection, acute pancreatitis, shock, and acidosis. Autopsy findings in the 7 patients who died included heavy airless lungs with microscopic evidence of hyperemia, capillary engorgement, interstitial and alveolar hemorrhage and alveolar atelectasis. Six of the 7 patients had hyaline membranes and evidence of a decrease in surfactant which was strikingly similar to the findings in neonatal respiratory distress syndrome. Thus, this syndrome was named "Respiratory Distress Syndrome in Adults". In 1969 the first breakthrough in therapy was reported when Ashbaugh used mechanical ventilation with positive end-expiratory pressure (PEEP) in the treatment of 21 patients (10). In 1971, Petty and Ashbaugh reviewed the clinical features and principals of management of this syndrome which they called the "Adult Respiratory Distress Syndrome" and used the abbreviation ARDS for the first time.

Although ARDS has been reported under a variety of names (congestive atelectasis, traumatic wet lung, pump lung, shock lung, DaNang lung, respirator lung, capillary leak syndrome, white lung, and adult hyaline membrane disease, among others), the uniformity of the clinical presentation has justified the use of a single term, ARDS, despite the variety of causes (11 - 13).

CLINICAL FEATURES OF ARDS

Definition

ARDS is a clinical and pathophysiologic entity and, as such, it must be defined on the basis of the clinical presentation of the patient and the extent of physiologic abnormalities. Criteria for diagnosing the adult respiratory distress syndrome are shown in Table 1 (14). Identification of ARDS begins with a catastrophic event which ultimately damages previously healthy lungs. The injury can be either direct pulmonary trauma or an indirect pulmonary injury such as shock. Clinically identifiable acute respiratory distress must be present. This is usually manifest by tachypnea and labored breathing with intercostal retraction and use of accessory muscles. Clinical exclusions include subacute and chronic infiltrative lung disease, and acute or chronic airflow limitations and primary left ventricular failure (15). The differentiation of cardiogenic and noncardiogenic pulmonary edema is critical and the use of a flow-directed catheter is indicated in many instances. For both clinical and research purposes, a pulmonary artery wedge pressure of 12 mm Hg or less should be included as part of the definition of the syndrome of ARDS.

Table 1

Diagnostic Criteria of ARDS

I. Clinical Setting

Clinical history of catastrophic event
- Pulmonary
- Nonpulmonary-shock, multisystem trauma

Clinical respiratory distress
- Tachypnea-greater than 20 breaths/minute
- Labored breathing

Exclusions
- Chronic pulmonary disease
- Left ventricular failure-PCWP less than 12 mm Hg

II. X-Ray Criteria

Diffuse pulmonary infiltrates
- Interstitial (initially)
- Alveolar (later)

III. Physiologic Criteria

PaO_2 less than 50 with F_IO_2 greater than 0.6
Total respiratory compliance less than 50 ml/cm-usually less than 20-30 ml/cm
Reduced FRC
Increased shunt fraction-(Q_S/Q_T) greater than 30 percent
Increased dead space ventilation-(V_D/V_T) greater than 60 percent

Radiographic abnormalities are entirely nonspecific but include a normal chest x-ray at the onset of the syndrome. As early as an hour or as late as two or four days after the precipitating insult, the chest x-ray will be noted to progress to interstitial and later diffuse alveolar infiltration.

Physiologic abnormalities focus on problems of oxygen transport and changes in lung mechanics. Severe hypoxemia is present (PaO_2 less than 50) in spite of high inspired oxygen fractions (F_IO_2 greater than 0.6). Lung and thoracic compliance is reduced, usually to 20 to 30 ml/centimeter (normal total respiratory compliance is 80 to 100 ml/centimeter). The mechanisms underlying these changes in compliance are complex and will be reviewed later in this discussion. Lung volumes are invariably reduced in ARDS (16-18). Functional residual capacity (FRC) is reduced and in many instances becomes less than the predicted residual volume. Both the shunt fraction and dead space ventilation are markedly increased, with shunt fraction exceeding 30% and dead space ventilation exceeding 60% of total minute ventilation.

Clinical Course

ARDS has a characteristic course that dates from the onset of the lung injury. Moore has recognized four distinct phases of progressive pulmonary insufficiency that may complicate hypoperfusion states associated with

nonthoracic trauma (19). Practical experience has shown that, with minor variations based on the initial insult, the same sequence of events is seen in patients with ARDS from any cause (Table 2).

Table 2

Clinical Course of ARDS

Phase 1 -- Acute Injury

- Treatment of shock and underlying disorder
- Hyperventilation and hypocapnia leading to alkalosis
- Mild lactic acidemia
- Tachypnea and dyspnea
- No auscultatory or X-ray evidence of pulmonary disease

Phase 2 -- Latent Period

- Patient clinically stable
- High cardiac output
- Adequate blood pressure and urine output
- Continuing hyperventilation, hypocapnia, dyspnea and tachypnea
- Increased intrapulmonary shunting-up to 20% of cardiac output
- Stiffening lungs
- Minor auscultatory and X-ray evidence of pulmonary disease

Phase 3 -- Acute Respiratory Failure

- Marked dyspnea and tachypnea
- Severe hypoxemia
- Mechanical ventilation with F_IO_2 greater than 0.5
- Decreasing lung compliance
- Diffuse rales
- Bilateral diffuse parenchymal infiltrates
- Marked increase in physiologic dead space

Phase 4 -- Severe Physiologic Abnormalities

- Gross intrapulmonary shunting-greater than 30% of cardiac output
- Severe hypoxemia unresponsive to therapy
- Metabolic and respiratory acidosis
- Secondary infections
- Impaired myocardial function
- Bradycardia, PVC's and finally asystole

Phase I includes the acute lung injury and the initial therapy. In the case of trauma, burns, or aspiration, the time of injury is known; however, the exact time of injury can be uncertain when sepsis or oxygen toxicity is the precipitating event. Shock is commonly present in this phase, requiring volume replacement and, at times, sympathomimetic agents for treatment. Spontaneous hyperventilation and its resultant hypocapnia occur despite an adequate PaO_2, producing respiratory alkalosis. Some patients may exhibit a concurrent mild lactic acidemia. In this phase, continued hyperventilation, tachypnea, and dyspnea, without auscultatory or roentgenographic evidence of pulmonary disease provide the initial indices of suspicion of impending respiratory complications.

Phase II develops in a period of relative physiologic stability and is sometimes called the latent period of ARDS. Cardiac output, blood pressure and urine output return to acceptable levels and the patient appears to be recovering. The length of this interval can be determined precisely after surgery or trauma and usually lasts from 6 to 48 hours. Signs of ARDS can appear insidiously when the time of the acute injury is not known. Despite apparently favorable trends, hyperventilation, hypocapnia, dyspnea and tachypnea persist. The venous admixture gradually increases to levels as high as 15 to 20% of the cardic output. While the lungs clinically appear to be stiff, only minor abnormalities can be detected upon examination of the chest or on a chest x-ray. The possibility exists that with proper treatment, ARDS is potentially reversible at this stage.

In Phase III, acute respiratory failure occurs. Dyspnea and tachypnea increase markedly and hypoxemia worsens despite the delivery of a high concentration of oxygen by face mask. Endotracheal intubation, mechanical ventilation, and a high concentration of inspired oxygen (usually greater than 50%) are needed to maintain an adequate level of arterial oxygen tension. Arterial carbon dioxide tension remains low, and acidosis is not significant, despite a slowly rising serum lactic acid concentration. Lung compliance decreases progressively, and as a consequence peak airway pressure increases. The combination of pulmonary shunting and diminishing compliance is indicative of a poor prognosis but often improvement may occur following the institution of positive end-expiratory pressure (PEEP) (20). The response to PEEP has prognostic significance, since those patients who have a rapid increase in PaO_2 after starting PEEP have a much lower mortality than those who do not improve or improve slowly over a period of hours (21).

The physical examination now is clearly abnormal. Diffuse, high-pitched, end-inspiratory crackles are heard diffusely over both lung fields. The heart sounds are normal. The chest x-ray is characterized by bilateral, diffuse, parenchymal infiltrates with a normal cardiac silhouette. Colonization of the respiratory tract by gram-negative organisms is frequent, but at least for a time there is no evidence of invasive pulmonary infection. Toward the end of the third phase, high arterial carbon dioxide levels reflect a marked increase in physiologic dead space and reduced alveolar ventilation. There is a compensatory rise in minute ventilation, which is frequently measured at well above 20 liters per minute.

Recovery can occur from this stage if the patient can be supported until lung function improves. Although high levels of inspired oxygen commonly are required to treat ARDS, these high concentrations of oxygen may increase the severity of the alveolar-capillary membrane injury as will be discussed later.

The fourth and final phase is recognized by gross intrapulmonary shunts in excess of 30% and severe hypoxemia refractory to therapy. Serum lactic acid levels increase, indicating tissue hypoxia. The rising $PaCO_2$ combined with the increasing serum lactate results in a metabolic and respiratory acidosis. Secondary pulmonary infection and sepsis are commonly seen and often are resistant to appropriate antibiotic therapy. Myocardial function is impaired by hypoxia and acidosis and hypotension and hypoperfusion ensue. Terminally, bradycardia, ventricular premature contractions, and finally asystole occur. In this final phase, the pathologic and physiologic derangements are essentially irreversible, despite the most heroic attempts to correct them.

CAUSES OF THE ADULT RESPIRATORY DISTRESS SYNDROME

The term cause has several meanings. In the context of ARDS, cause can refer to: (A) an initiating clinical event or (B) a mechanism which mediates the lung injury. The initiating clinical event can directly lead to lung injury such as aspiration of gastric contents, or can be indirect such as multiple trauma or sepsis. It can be difficult to distinquish a mechanism which mediates lung injury from other pathophysiologic processes which, like ARDS, may be associated with the primary clinical event. The role of disseminated intravascular coagulation (DIC) is an example of such a dilemma. Whether DIC is a mechanism resulting in lung injury or simply an associated abnormality with no clear etiologic role in the pulmonary process is not clear. In this section I will focus primarily on the initiating event and its recognition as the cause of ARDS.

A compiled list of causes of ARDS have been published by several authors (22, 23). Several problems exist with such lists. One problem is whether the associated pulmonary process actually represents ARDS. An example of this is lymphangitic carcinomatosis. This entity is included by several authors as a cause of ARDS. While this disease entity can have several features similar to ARDS, the pulmonary pathologic process has such specific differences that I question whether this clinical entity should be lumped under the heading of ARDS. Another problem is that lists of causes of ARDS fail to differentiate common from obscure causes.

Table 3

Etiologic Factors Associated with the Adult Respiratory Distress Syndrome in 100 Consecutive Patients

Factors	Single Cause	Multiple Cause Combination	Total (%)
Common	23 Patients	66 Patients	
Sepsis	9	16	25
Shock	2	22	24
Trauma	2	21	23
Fluid overload	2	19	21
Aspiration	2	13	15
Diffuse infectious pneumonia	6	4	10
DIC syndrome	0	8	8
Fat embolism	0	7	7
Uncommon	7 Patients	4 Patients	
Drug overdose	2		
Drowning	2		
Pulmonary embolism and transplant	0	2	
Hemorrhage and transplant	0	2	
Air embolus	1		
Pancreatitis	1		
Inhaled irritant	1		

Petty, Sem. Respir. Med. 3:219, 1982

Perhaps the best data recording the causes of ARDS is that recently reported by Petty and colleagues (14). Patients were selected consecutively by this group using the criteria defining ARDS shown in Table 1. The etiologic factors underlying these cases were analyzed and classified as common and uncommon causes. As shown in Table 3, although some patients had a single etiologic factor, in the majority, there was a combination of causes. A total of 57 different combinations of etiologic factors was found in this group of patients. Sepsis, shock, trauma, fluid overload, aspiration of gastric contents and diffuse infectious pneumonia were among the most common etiologic events. This study indicates the problems inherent in categorizing patients with ARDS by a specific or single etiology. Thus, until a marker of the syndrome is found or the mechanism can be determined and identified, ARDS will remain a clinical syndrome with multiple causes.

CHARACTERISTICS OF THE LUNG INJURY IN ARDS

The term "injury" usually implies alteration in structure which can be demonstrated by either a light or an electron microscope. In both humans with ARDS and in animal models of the syndrome, severe alterations in lung structure occur. However, the relationship between these structural alterations and alterations in function are largely intuitive. It is not clear whether the initial injury to the lung is an alteration in structure; nor is it clear that the observed alterations fully explain the functional abnormalities.

In some instances functional injury occurs in the absence of demonstrable structural changes. Increases in lung vascular permeability and pulmonary edema can be demonstrated by physiologic measurements following several experimental interventions in which the structural alterations are difficult to demonstrate (24-26). Because there may be functional injury in the absence of demonstrable structural injury, we will review both pathological and physiological evidence in an attempt to detail the lung injury which is seen in this syndrome. Utilizing this as a basis, we will then explore the pathogenesis of the alterations in lung function which may eventuate in the group of abnormalities labeled the Adult Respiratory Distress Syndrome.

Pathology

The most important pathological studies available in patients with ARDS arose from a somewhat unlikely source. Because of technical advances in extracorporeal membrane oxygenation and reports of long term survival of patients with ARDS treated with this technique, the National Heart and Lung Institute undertook a multicenter prospective collaborative study of patients with severe ARDS between 1975 and 1977 to determine whether such therapy would reduce mortality from ARDS (27). The study convincingly demonstrated that extracorporeal membrane oxygenation had no clinical benefit. This study, however, remains an important landmark in the investigation of ARDS, since it involved the first large series of patients with ARDS who were meticulously investigated before and after death. The results of this study prompted a major shift in investigative attention in ARDS because they clearly demonstrated that changes in the architecture of the lung that had previously been thought to take weeks or months, progressed rapidly during cardiopulmonary support, usually causing death within 3 weeks (28).

Pulmonary biopsy samples obtained before and after death from patients with ARDS in the study of membrane oxygenation and several smaller studies reveal that the lung's response to an insult and subsequent repair of the injured tissue can be divided into three phases: (A) the early exudative phase, (B) the subsequent cellular proliferative phase and (C) the fibrotic proliferative phase (29-31). These studies clearly revealed that the conceptual description of ARDS as a simple "capillary leak" was over-simplified.

Exudative Phase: The earliest lesions in patients with ARDS are alveolar and interstitial edema (32). The alveolar septum is thickened due to capillary congestion and the movement of red cells and inflammatory cells into the interstitium. The alveolar spaces are inhomogeneously filled with a proteinaceous and often hemorrhagic fluid containing white blood cells, macrophages, cell fragments and amorphous material composed of plasma proteins, cell debris, fibrin strands and the remnants of surfactant. Damage to type I alveolar cells varies, ranging from slight swelling to total destruction of the cells (33). Early hyaline membranes composed of protein, fibrin strands and cell debris can be seen mainly in the alveolar ducts and respiratory bronchioles. While increased permeability of the capillary endothelium has been documented with ARDS associated with sepsis (34), pathologically, no large intercellular gaps, or areas of complete capillary destruction are noted (33). Thus, it would appear that increased alveolar capillary membrane permeability can occur with minimal structural change in capillary endothelial cells.

Cellular Proliferative Phase: After the initial edematous response to injury, there is a striking proliferation of type II alveolar cells, which at times form a continuous layer covering the previously denuded basement membrane. The reason for this abundant augmentation of type II alveolar cells shortly after an acute alveolar injury is believed to be their stem-cell function for the entire epithelium. It is believed that their proliferation is the first step of the protracted two stage repair process for the squamous alveolar lining. The second step of the repair process involves the transdifferentiation of proliferated type II cells into squamous type I cells, thus forming a new alveolar epithelium (35). The alveolar septum in this phase is 5 to 10 times thicker than normal and is infiltrated by leukocytes, plasma cells and histiocytes (33). Alveolar edema is less extensive at this stage but the endothelial injury becomes more apparent than it was in the acute phase. Hyaline membranes present in the acute phase begin to organize, with proliferation of fibroblasts and infiltration with inflammatory cells (32).

Fibrotic Proliferative Phase: After only 7 to 10 days, fibrotic changes begin to occur in both the alveolar septum and hyaline membranes. The protein-rich alveolar edema fluid is organized by loose fibrous connective tissue to create a pattern of intra-alveolar fibrosis (36). The delicate alveolar structure is no longer recognizable as fibroblasts become predominant in the cellular infiltration of the alveolar septum. The combination of these two processes may combine to form massive tissue plates which completely mask the original architecture of the lung parenchyma. Hyaline membranes are replaced by fibroblasts and are transformed to fibrous tissue with the most apparent changes being found in the alveolar ducts and respiratory bronchioles. Alveolar duct fibrosis is a characteristic lesion in patients who die after prolonged respiratory distress (28, 32). Pratt, et al., believed that these fibrotic changes were the major factor responsible for death in 80% of the patients dying after 2 or more weeks of therapy (28) (Table 4).

Table 4

Pathology in ARDS

Exudative Phase (24-96 hours)

- Alveolar and interstitial edema
- Capillary congestion
- Destruction of Type I alveolar cells
- Early hyaline membrane formation

Proliferative Phase, Cellular (3-10 days)

- Increased Type II alveolar cells
- Cellular infiltrate of the alveolar septum
- Organization of hyaline membranes

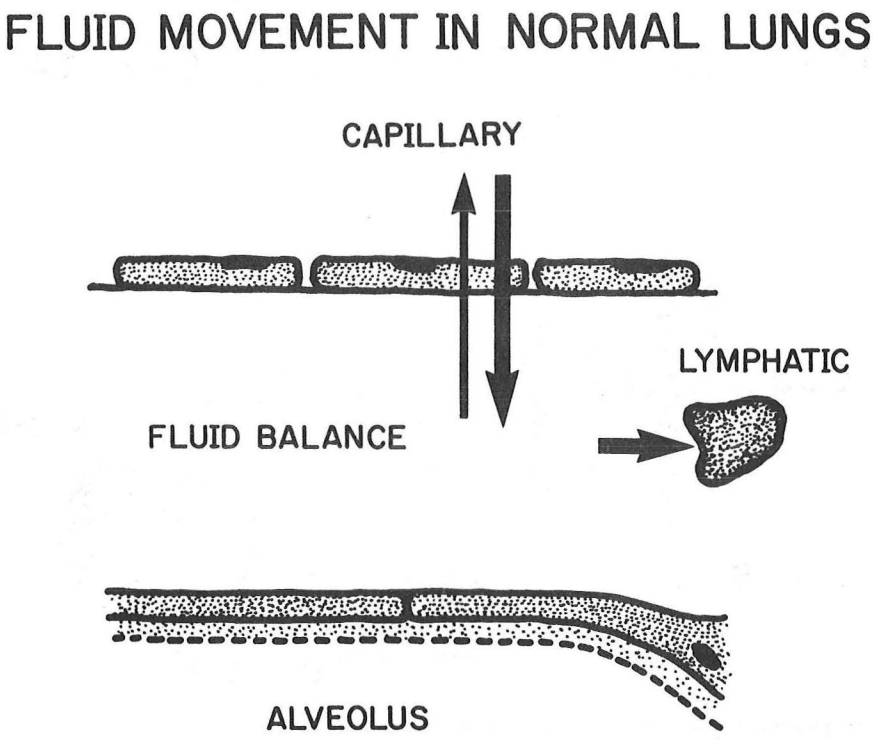
Proliferative Phase, Fibrotic (greater than 7-10 days)

- Fibrosis of hyaline membranes and alveolar septum
- Alveolar duct fibrosis, typical lesion

Functional or Physiologic Injury

Microvascular Injury: Pulmonary edema, that is, excess accumulation of fluid in the lungs, has generally been considered a basic abnormality in ARDS (37-39). The clinical diagnosis of the syndrome is made by demonstrating pulmonary edema in the presence of low left heart pressures. Since pulmonary edema occurs in the absence of an elevated hydrostatic pressure in the exchange vessels in the lung, it is inferred that exchange vessels in the lung are leaking excessively; that is, that vascular permeability is increased.

Figure 1

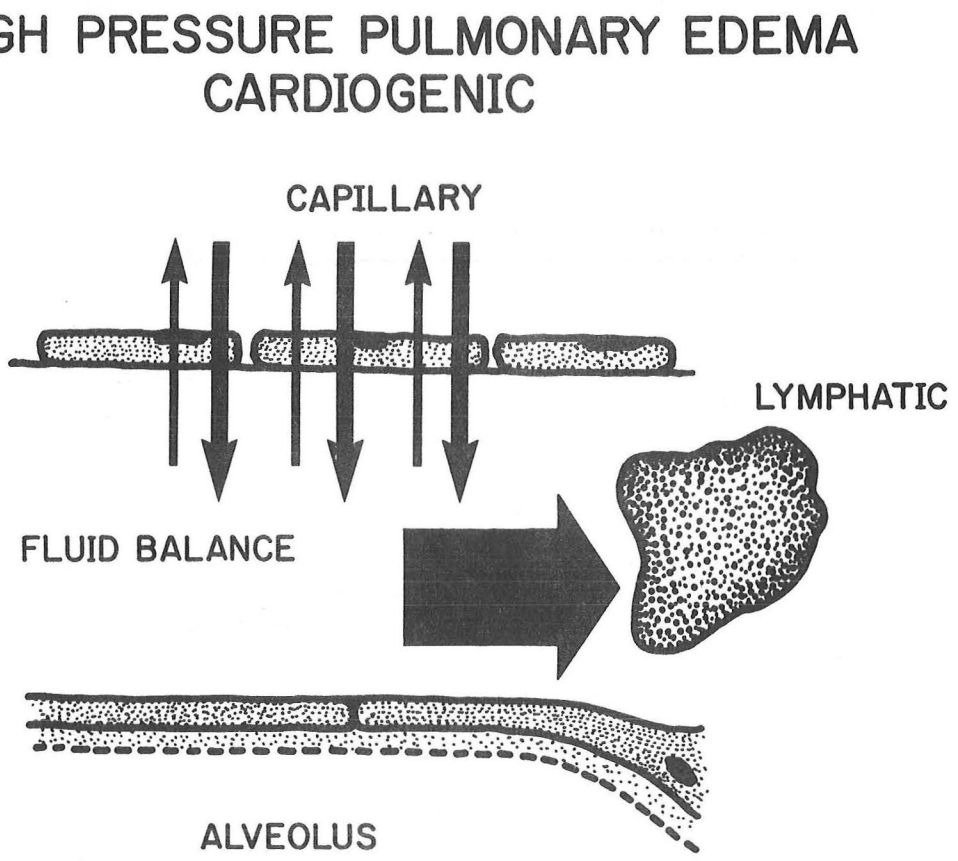


A brief review of the fluid exchanging properties of the normal lung are shown in Figure 1. The microvascular endothelial membrane is on the vascular side of the gas exchange unit, and is permeable to fluid and relatively impermeable to protein. The alveolar epithelial membrane and surfactant are in contact with the external environment. The alveolar epithelial membrane is relatively impermeable to fluid and protein in the normal state. The interstitium is the space bound by these two membranes. In the normal lung, fluid filtration across the microvascular membrane of the alveolar septal capillary and postcapillary venules results in accumulation of fluid in the interstitial spaces (40, 41). This interstitial fluid is in equilibrium with the vascular space. This equilibrium is governed by factors expressed in the familiar Starling equation: $\dot{Q}_f = K_W [(P_C - P_i) - \sigma_S (\pi_C - \pi_i)]$. A description of the symbols is as follows: $\dot{Q}_f$ = Net exchange of fluid across membrane; K_W = Filtration coefficient of water; P_C = Capillary hydrostatic pressure; P_i = Interstitial

hydrostatic pressure; σ_s = Reflection coefficient of solute; π_c = Capillary osmotic pressure; π_i = Interstitial osmotic pressure.

The end result of the forces acting in the Starling equation, in the normal lung, is a small net movement of fluid out of the vascular system and into the interstitium. Under normal circumstances, this fluid is readily dealt with by the lymphatic system, a series of tubular structures which carries the protein containing acellular filtrate back into the vascular system. Since the alveolar epitheilium is relatively impermeable to water and protein, the fluid does not gain access to the alveoli.

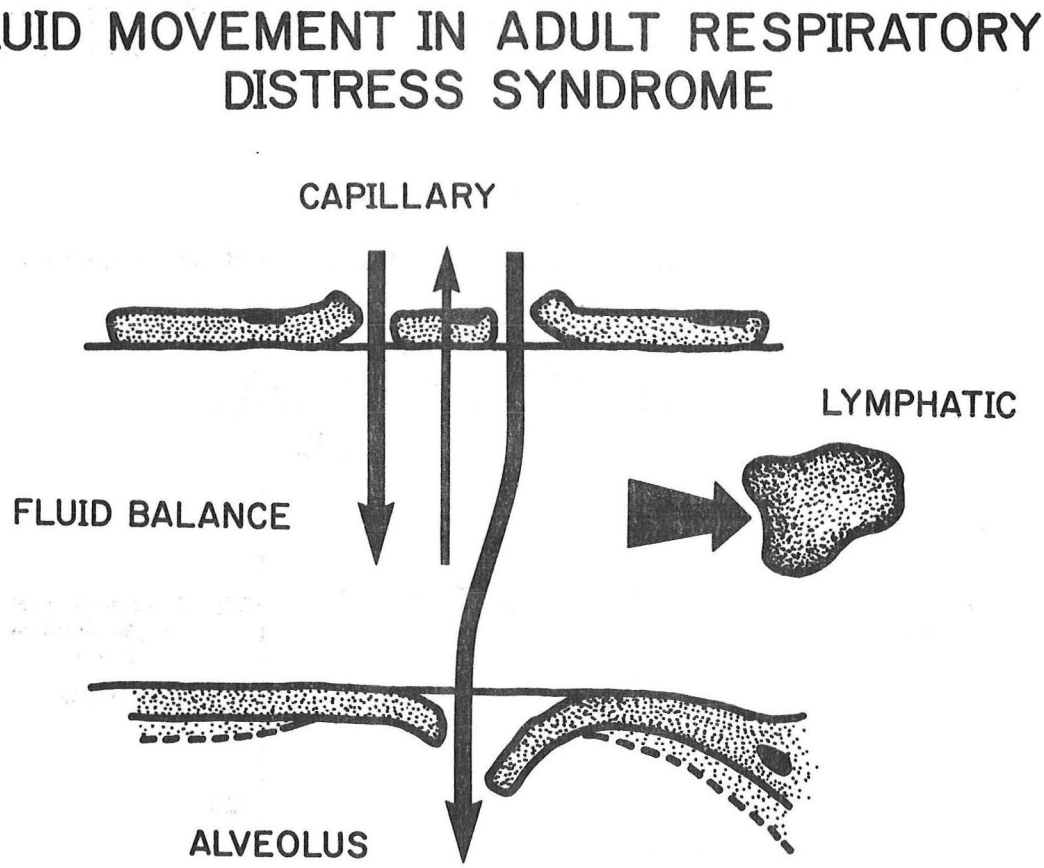
Figure 2



The fluid exchanging properties of the lung in cardiogenic pulmonary edema are shown in Figure 2. As shown in this diagram, the integrity of the microvascular barrier is normal, as represented by the same size and number of pores in the endothelium. However, any factor that increases the sum of pressure will increase the outward filtration of fluid. When microvascular hydrostatic pressure rises rapidly, the increased driving pressure increases filtration of fluids and washes out protein from the perimicrovascular interstitium. The flow of lymph from the lung rises and eventually reaches a

new steady state level. The interstitial concentration of protein and, consequently, the perimicrovascular osmotic pressure decreases because, with normal integrity of the endothelial barrier, leakage of protein is markedly restricted relative to the flow of water. Unless pressure rises are severe, the alveolar space once again remains free of fluid (42-44).

Figure 3



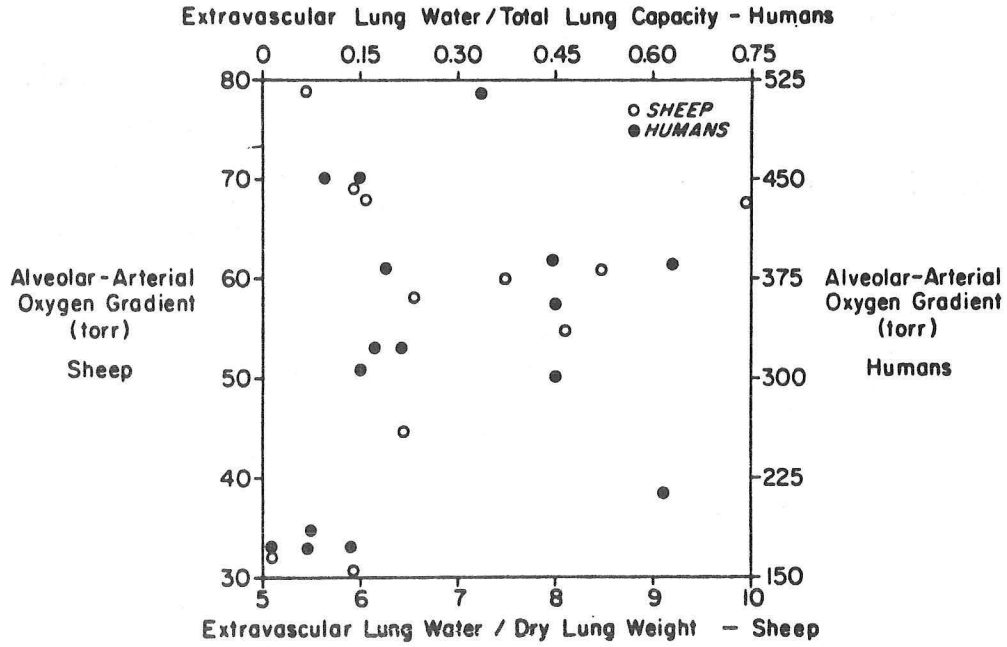
The fluid exchanging properties of the lung in ARDS are shown in Figure 3. In ARDS, the integrity of the endothelial and epithelial barriers is compromised. This is represented by a increase in the size of the pores in the endothelial membrane and by a rent in the integrity of the alveolar epithelial membrane. For the same hydrostatic driving pressure, the flow of lymph is greatly increased and the perimicrovascular concentration of protein is high. The alveolar epithelial membrane injury allows both water and protein to gain access to the alveolar space.

Increased vascular permeability in the lung has been directly demonstrated in animal studies with experimental insults similar to those which cause ARDS in humans. Brigham, using a sheep chronic lung lymph fistula model, has demonstrated an increased permeability to protein in the pulmonary microvasculature of animals given *E. coli* endotoxin (26). Similar results have

been found using other bacteria and following pulmonary oxygen toxicity (25, 45). Thus, a blood borne, bacteria-related product that increases the lung's permeability to protein has been identified. Evidence for increased lung vascular permeability in humans is less direct but evidence does exist that permeability is altered. Anderson, et al., have demonstrated increased permeability in septic patients with ARDS compared with patients with cardiogenic pulmonary edema (46). Additionally, the presence of edema in the absence of elevated pressures in the lung circulation and the more direct measurements of solute exchange between the intravascular and extravascular spaces of the lungs, strongly suggest that increased lung vascular permeability is the reason pulmonary edema develops in this syndrome (47). It should be pointed out that the animal models of increased microvascular permeability do not have similar morphology and physiology to that found in human ARDS.

Figure 4

Relationship Between Extravascular Lung Water and Gas Exchange

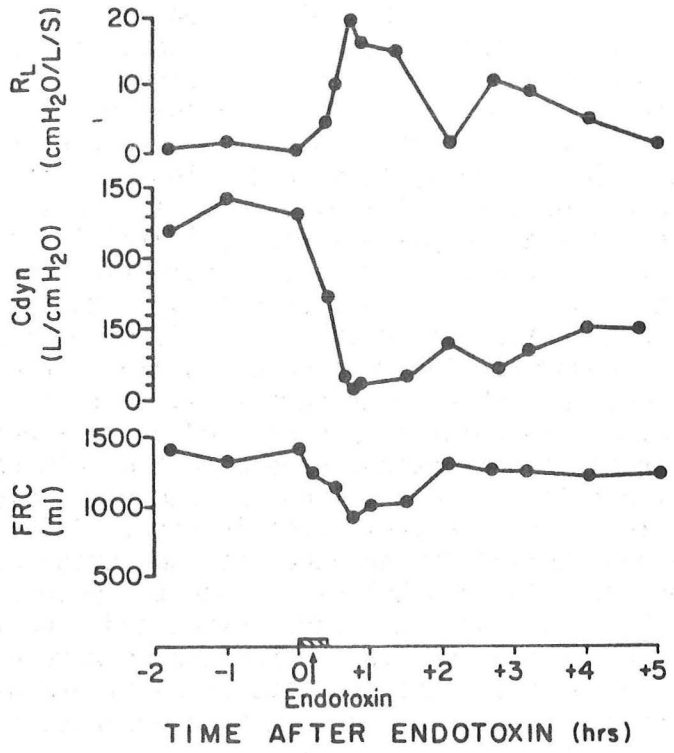


Altered Vascular Reactivity: Although pulmonary edema presumably resulting from microvascular injury occurs uniformly in the adult respiratory distress syndrome, there is good evidence that edema alone is insufficient to explain the magnitude of hypoxemia (48). The relationship between extravascular lung water and gas exchange is shown in Figure 4. This graph plots data from sheep following endotoxin infusion, shown as open circles, and data from humans with a clinical diagnosis of ARDS. Lung water measurements in sheep were post mortem, and lung water measurements in humans were made using a single pass indicator dilution isotope technique. As can be seen, there is no correlation between the severity of the gas exchange abnormality and the amount of water

in the lungs (48). One possible explanation of the findings mentioned above may be found in animal experiments in which Gram-negative endotoxin has been shown to prevent pulmonary vasoconstriction resulting from alveolar hypoxia (49). It is presumed that localized hypoxia produces localized vasoconstriction and that this is an important phenomenon in matching perfusion to ventilation. If the ability of the pulmonary vascular bed to react locally to hypoxemia were prevented, then poorly ventilated or nonventilated areas of lung would be perfused, resulting in intrapulmonary shunting and hypoxemia. Although it is difficult if not impossible to test this hypothesis in humans with respiratory failure, animal evidence suggest that loss of hypoxic vasoconstriction with pulmonary injury may be an important part in the pathogenesis of hypoxemia in ARDS.

Figure 5

The Effects of *E. coli* Endotoxin Infusion on Lung Mechanics



Altered Airway Functions: Changes in lung mechanics, specifically decreased lung compliance and decreased functional residual capacity are typical of ARDS (18). Whether changes in lung mechanics result from the primary injury or are secondary to pulmonary edema is not easy to answer in the clinical setting. Animal studies reveal that alterations in airway function occur independent of the pulmonary edema. Figure 5 shows measurements of resistance to airflow across the lungs, lung compliance and functional residual capacity over several hours following the infusion of *E. coli* endotoxin into sheep (50). Early after endotoxemia, there is a dramatic increase in resistance to airflow and

a fall in lung compliance and FRC. With time, resistance to airflow decreases and FRC rises. Lung compliance remains low for several hours. The early phase of this response is prior to the time when pulmonary edema develops so that the increase in resistance to airflow is not explained by edema. Since Gram-negative endotoxemia is a common clinical setting in which ARDS develops, these data may imply that primary abnormalities in airway function occur in humans with ARDS.

These changes could be important in further explaining the hypoxemia seen in ARDS. Increased resistance to airflow across the lungs and decreased lung compliance may result in abnormal distribution of ventilation, disturbing the matching of ventilation and perfusion and contributing to hypoxemia.

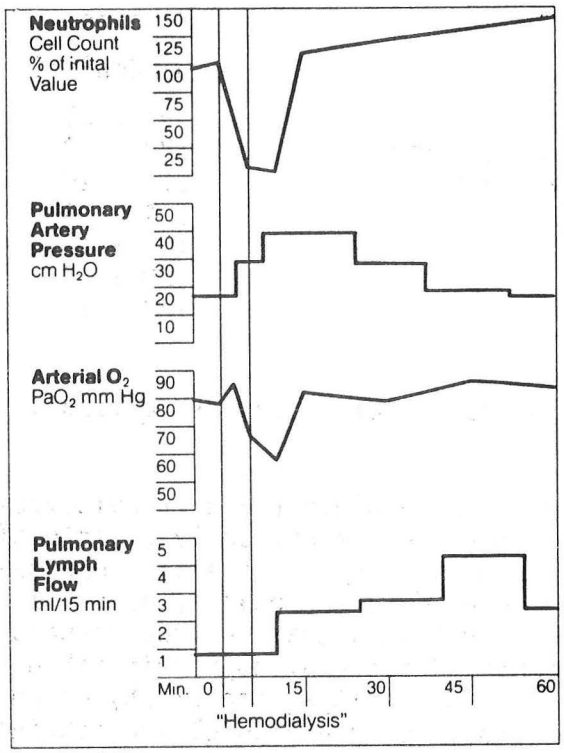
PATHOGENESIS OF ACUTE PULMONARY ENDOTHELIAL INJURY

Complement, Neutrophils and Proteases

Initial insight into the potential importance of endothelial injury by neutrophils arose from an unlikely source. In 1968, Kaplow and Goffinet noted that sudden and transient neutropenia occurred during cellophane membrane hemodialysis (51). Additionally, in a substantial proportion of those who were repeatedly dialyzed for more than three years, a peculiar pulmonary fibrosis-calcinosis syndrome also developed (52). Neutrophils were found to be aggregated and deposited in the pulmonary microvasculature during this neutropenic interval (53). These disparate phenomena have been shown to be related and are believed to be caused by chaotic complement activation as a result of exposure to the cellophane of the dialyzer coil. Unlike the situation with antibody-mediated activation, complement was activated in the hemodialysis apparatus via the alternative pathway. Complement activation could reproduce all of the above phenomena and the probable leukocyte aggregant was identified as the peptide fragment, C5a or its metabolite (54). Since similar, albeit more pronounced, pulmonary abnormalities were noted in ARDS, Craddock, et al., infused activated complement into sheep with chronic lymph fistulas (55). As shown in Figure 6, activated complement components induced a marked neutropenia, severe pulmonary artery hypertension, hypoxemia and pulmonary edema as detected by excessive lymph efflux from the lungs of these animals. Most intriguingly, the edema fluid was relatively protein-rich. This finding suggested that pulmonary endothelial damage occurred when granulocytes were sequestered in close apposition to endothelium. Since the pulmonary abnormalities of microvascular plugging with granulocytes and monocytes, high-protein pulmonary edema, and pulmonary artery hypertension were all characteristic of ARDS, it seemed possible that the etiologies of hemodialysis lung dysfunction and ARDS might be the same although more pronounced in the latter case.

Figure 6

Pulmonary Leukostasis in Hemodialysis



The *in vitro* mechanism by which activated complement promotes granulocyte plugging of the pulmonary microvasculature has also been studied (54). One activated complement component, C5a, was found to potently aggregate granulocytes when added to them in stirred suspension. In further *in vitro* studies, complement-granulocyte interactions were shown to injure endothelial cells in tissue culture as shown in Table 5. Endothelial damage, measured by chromium 51 release, can be demonstrated to occur when cultured endothelial cells are exposed to granulocytes plus activated complement but not when endothelial cells are exposed to granulocytes plus normal or heat-inactivated serum, or when endothelial cells are exposed to activated complement alone. Further, the active complement component was shown to be C5a, in that damage resulted when granulocytes plus C5a were added to endothelial cell cultures, but did not occur when C3a was added or when an anti-C5 antibody was added in addition to the C5a (56).

Table 5

Effects of Complement-Activated Granulocytes on Cultured Endothelial Cells

Additions To Endothelial Cells	^{51}Cr Release	P Value
	% of Control	
Activated C + PMN	191 ± 29	< 0.01
Heat-Inactivated C + PMN	120 ± 9	NS
Untreated Sera + PMN	115 ± 10	NS
Activated C	104 ± 4	NS
C5a + PMN	186 ± 17	< 0.0025
C5a + Anti-C5a + PMN	120 ± 6	NS
C3a + PMN	127 ± 11	NS

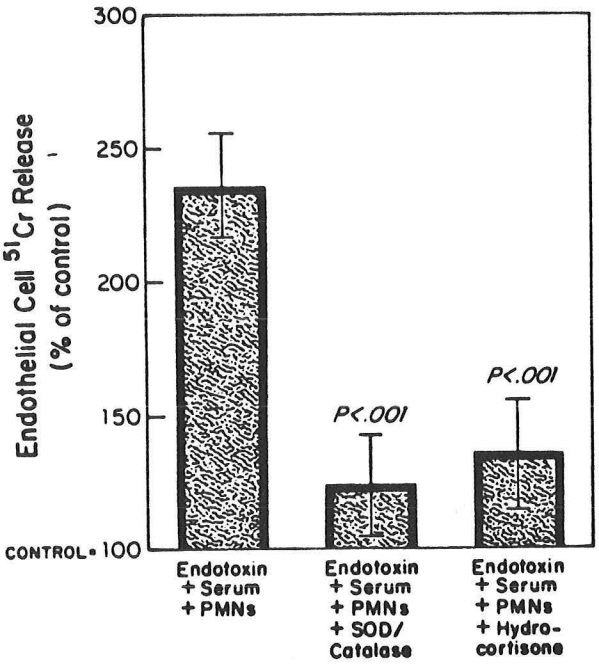
Sacks, J. Clin. Invest. 61:1161, 1978

The mechanisms by which complement and granulocytes injure the lung are uncertain, but granulocytes are theoretically capable of causing both endothelial and interstitial injury. Granulocytes liberate superoxide radicals and other highly reactive oxidant byproducts of phagocytosis. In addition, neutrophils produce neutral and acid proteases that destroy structural proteins such as collagen, elastin, and the adhesive glycoprotein fibronectin, which seems to be necessary to order the interstitial topography of cells and connective tissue (57-59). These proteases can also cleave fibrinogen, the Hageman factor, complement, and other plasma proteins. Thus, neutrophil proteases can both destroy interstitial architecture and permit local amplification of lung injury by activating plasma precursors that ultimately result in further leukocyte aggregation and intravascular coagulation.

The mechanism by which the combination of activated complement and granulocytes damages pulmonary endothelium has been studied utilizing cultured endothelial cells (56). Endotoxin was found to have the same effects *in vitro* as the addition of activated complement components (60). As shown in Figure 7, a brief exposure to granulocytes and endotoxin results in endothelial damage. This damage was appreciably inhibited by toxic oxygen radical dissipators, superoxide dismutase (SOD) and catalase. Additionally, hydrocortisone blocked this *in vitro* injury.

Figure 7

Effects of Endotoxin on Endothelial Cells



Recent clinical studies also confirm the relevance of these theoretical considerations to ARDS. Two recent studies using bronchoalveolar lavage technique have shown that greater than 80% of the recoverable bronchoalveolar cells are neutrophils whereas neutrophils comprise less than 1% of the bronchoalveolar lavage population in normals. Additionally, a potent protease, leukocyte elastase, has been found in some patients with ARDS (61, 62). Elastase activities from patients with ARDS as well as other pulmonary diseases are shown in Table 6. Free elastase activity was observed in 62% of patients with ARDS, none of 23 normal, non-smoking patients, and 12% of smoking normal patients.

Table 6

Elastase Activity in BAL Fluids

Group	Total Number Subjects	Elastase Activity in BAL Fluids
		% Positive
ARDS	47	62
Nonsmoking normals	23	0
Smoking normals	17	12
COPD	30	13
Pneumonia	37	46
Carcinoma	27	7

McGuire, J. Clin. Invest. 69:543, 1982
Lee, N. Engl. J. Med. 304:192, 1981

It is of interest that the presence of elastase was found to be more frequent in ARDS than in COPD or in bronchopneumonia. While the presence of free elastase is not specific for ARDS and the sample size is not large, these studies suggest that in ARDS the release of enzymes by granulocytes is heightened or that inhibition of the released enzymes by anti-proteases is diminished.

Futher studies have evaluated the status of anti-proteases in the lungs of patients with ARDS. In all cases where protease activity was not detected in the bronchoalveolar lavage fluid of ARDS patients, α1-protease inhibitor (α1-PI) was found both immunologically and by functional testing. In these patients, complexing of the α1-PI and leukocytic elastase was suggested in immunoelectrophoresis studies in which co-migration of elastase and α1-PI occurred. In an additional group of patients, protease and free α1-PI were found. In all these cases α1-PI was inactive (62).

The factors responsible for the inactivation of free α1-PI are not clear. One of the most plausible mechanisms to account for the inactivation is contact with oxidizing agents. α1-PI activity is inhibited by oxidation of a methionyl residue at the reactive center of the molecule (63, 64). Assuming that neutrophils are stimulated to release elastase in ARDS, it is altogether possible that they generate superoxide anion, H_2O_2, and $\cdot OH^-$ as well. In addition, myeloperoxidase, which is released from stimulated leukocytes, inactivates α1-PI in the presence of H_2O_2 and chloride ion (65). Each of these could bring about the oxidation of the methionyl residue in the reactive center of the α1-PI.

Clinical studies have also confirmed the relevance of complement activation to development of ARDS. A significant correlation between neutrophil aggregating activity in plasma, presumably secondary to C5a, and the later development of ARDS in patients with a wide variety of insults has been reported as shown in Table 7 (66). Of the 61 patients studied, 33 developed a syndrome of ARDS and 28 did not. Thirty-one of the 33 patients ultimately

developing ARDS had positive assays, whereas only 5 of the 28 patients not developing ARDS were positive. This correlation persisted even if septic patients were excluded from analysis. In the nonseptic subset, 18 of 19 developing ARDS had positive C5a assays; only 3 positive assays were observed among 26 patients who did not develop ARDS.

Thirty-one patients had serial plasmas collected over several days beginning with the time that high risk for ARDS was recognized. Only 6 of the ARDS patients were included in this group. In this group of patients, all patients who eventually developed ARDS had positive C5a assays and none of of the patients not developing ARDS were positive. Five of the 6 positive patients had a positive C5a assayed 8 hours or more before ARDS could be diagnosed clinically.

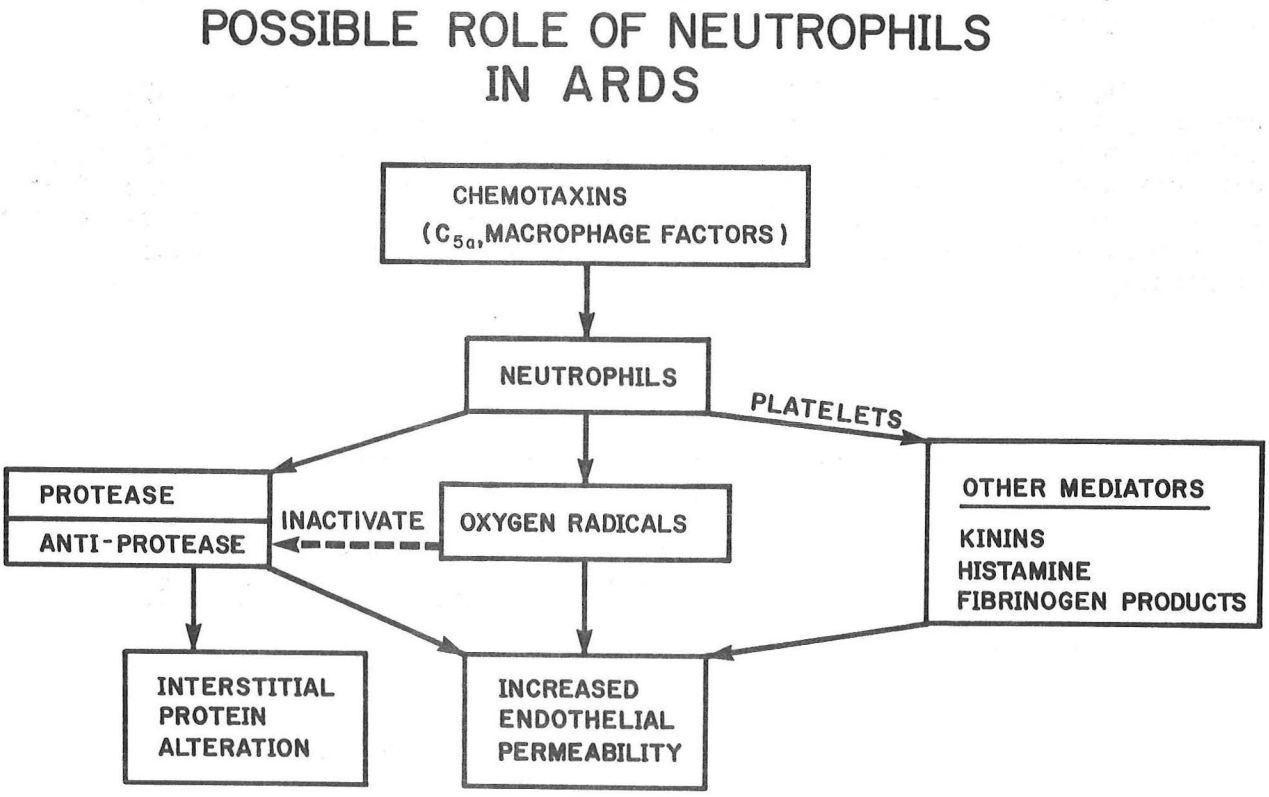
Table 7

Association of Positive Plasma C5a Assays with Development of ARDS

C5a	All Patients		Patients Without Sepsis	
	ARDS	No ARDS	ARDS	No ARDS
Positive	31	5	18	3
Negative	2	23	1	23
	$p < 0.00001$		$p < 0.00001$	

From these diverse observations, the hypothesis has been advanced that ARDS is mediated by complement, granulocytes and proteases (Figure 8).

Figure 8



It is proposed that ARDS is preceded by complement activation, a common consequence of trauma, sepsis and other predisposing events. Complement activation generates C5a, which causes leukocyte aggregation in the lungs. Aggregated neutrophils injure endothelial cells by the generation of toxic oxygen radicals. The neutrophils also liberate proteases that destroy structural proteins, such as collagen, elastin and fibronectin, and promote further local inflammatory changes by proteolysis of circulating plasma proteins, such as Hageman factor, fibrinogen, and complement, while pulmonary anti-proteases are inactivated by oxygen radicals released from immune effector cells and potentially by a therapeutic hyperoxic environment.

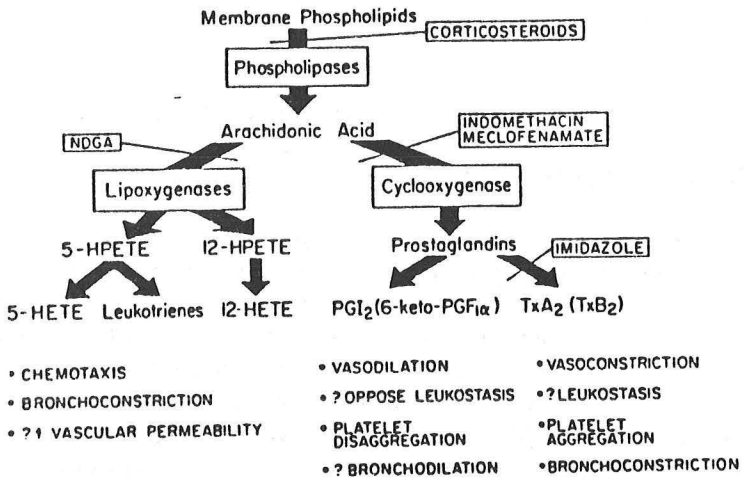
This scenario is intellectually pleasing, and may in fact represent a first approximation of the mechanisms responsible for acute endothelial damage and interstitial disruption in ARDS. First, several studies have suggested that the leukocyte is not essential for the production of lung injury in all forms of pulmonary edema which are associated with the aggregation of neutrophils in the lung (67, 68). Secondly, while certain pulmonary function test were affected and a widened A-aO_2 gradient did emerge in the studies of Jacobs and associates, frank pulmonary edema did not ensue and the abnormalities of mechanics and hypoxemia were short-lived (55). Futhermore, infusion of purified C5a into animals other than sheep, i.e. rabbits, causes only a transient neutrophil sequestration in the pulmonary microvasculature. This sequestration is reversible and does not lead to neutrophil migration through microvascular walls or to a frank permeability pulmonary edema (69). Thirdly, while neutrophils from patients with ARDS have enhanced aggregation *in vitro*, this finding does not prove that C5a is the responsible agent *in vivo* because several different classes of chemicals will aggregate neutrophils *in vitro* (70). Clearly, the pulmonary consequences of complement infusions in animals do not progress to the severe architectural derangement seen in patients with ARDS. It appears then that while neutrophils may be involved in the acute lung injury of ARDS, an additional stimulus is required besides simply that causing neutrophil sequestration in the lungs.

Prostaglandins in Acute Lung Injury

The role of prostaglandins in the pathogensis of ARDS is uncertain. There are, however, several reasons to predict their involvement. First arachidonate metabolites, especially the prostaglandins, have been shown to be vasoactive in the lung circulation (71, 72). Additionally, a number of interventions in animals which are similar to those resulting in ARDS cause the lung to release increased amounts of cylo-oxygenase metabolites of arachidonate (73-75). Increased lung lymph concentration of thromboxane B_2, 6-keto-$PGF_{1\alpha}$ (the principal metabolite of prostacyclin) have been shown in sheep following infusion of *E. coli* endotoxin.

Figure 9

Arachidonic Acid Metabolism



An abbreviated scheme of arachidonate metabolism is shown in Figure 9. Normally, arachidonate exists bound to phospholipids of cell membranes. Injury, through the action of phospholipases, results in the release of phospholipids from cell membranes. This results in the liberation of free arachidonic acid. The arachidonic acid can serve as a substrate for production of prostaglandins and thromboxanes through a cyclo-oxygenase enzyme and as a substrate for the production of several hydroxy fatty acids and leukotrienes, which have biological activity, through the action of a lipoxygenase enzyme. Since several of these substances have been shown to be present in the setting of acute lung injury, we will briefly review their potential involvement in the pathogensis of acute lung injury.

Since some thromboxanes are potent smooth muscle constrictors, and since pulmonary vasoconstriction is a prominent part of the pathophysiology of the early response to endotoxemia, it is tempting to postulate that the pulmonary vasoconstriction is mediated by endogenous production of thromboxane A_2. In addition, marked increases in airway resistance also occur early after infusion of endotoxin and appear coincident with pulmonary vasoconstriction. Thromboxane might also mediate these effects (50). Further evidence for their involvement in this regard comes from studies in which cyclo-oxygenase inhibitors were utilized. The early pulmonary hypertension and increased resistance to airflow across the lungs were both inhibited by meclofenamate and indomethacin. The decrease in lung compliance which occurs later was not, however, inhibited by this treatment, nor was the later increase in lung vascular permeability. These studies suggest that the early bronchoconstriction and vasoconstriction in the lung following endotoxemia may well be mediated by cylo-oxygenase products of arachidonic acid (50).

Other cylo-oxygenase metabolites of arachidonic acid are vasodilators. The most potent vasodilator known in the lung circulation is prostacyclin (76). While available evidence suggests that prostaglandins do not alter lung vascular permeability per se, Reaves and co-workers have hypothesized that this vasodilator may be responsible for the loss of hypoxic pulmonary vasoconstriction during endotoxemia. These investigators have shown that during the late phase after endotoxemia, hypoxic vasoconstriction is absent but that the response can be restored by treatment with cylo-oxygenase inhibitors (49). Additionally, they have shown that infusion of arachidonic acid during hypoxic vasoconstriction results in vasodilation coincident with increased lung production of prostacyclin metabolites (77). Additional studies have shown improvement in gas exchange following lung injury in the presence of cylo-oxygenase inhibitors (50).

In summary, cylo-oxygenase metabolites of arachidonic acid may mediate pulmonary vasoconstriction, airway constriction, and loss of hypoxic pulmonary vasoconstriction i.e., by vasodilator influences.

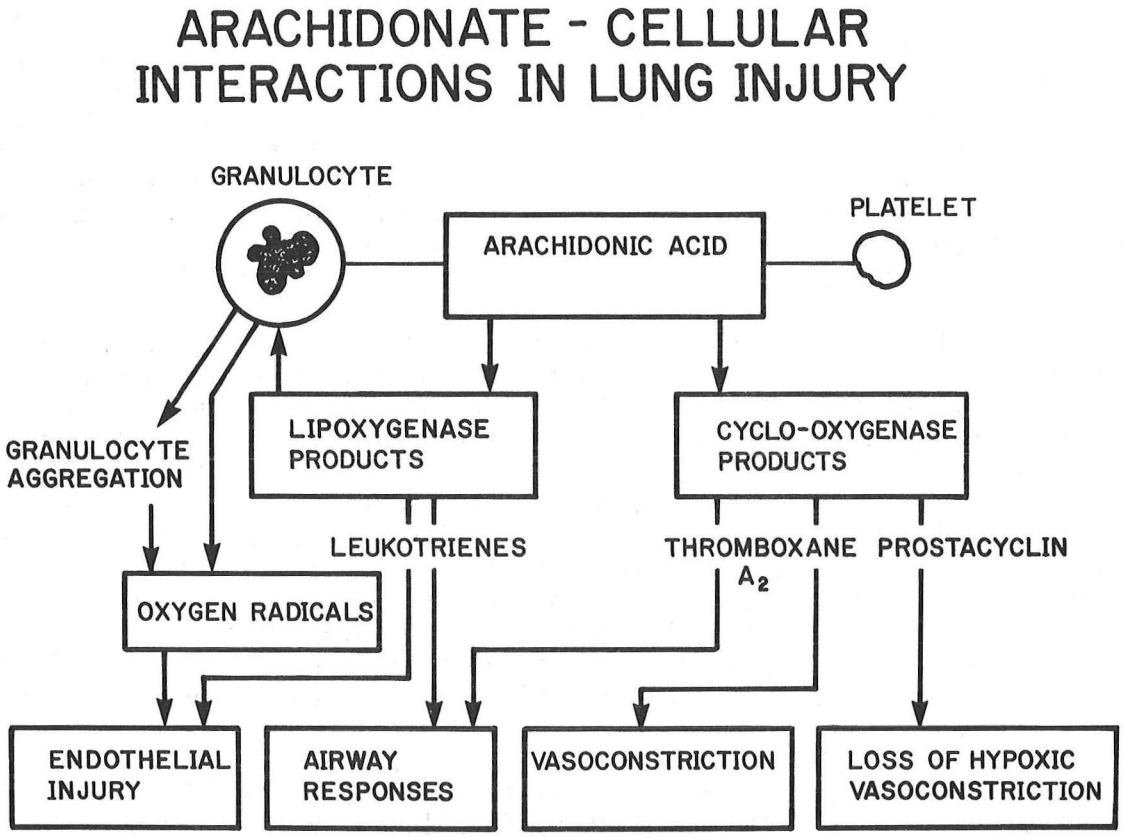
Recent attention has focused on lipoxygenase products of arachidonate, because these hydroxy fatty acids are potent granulocyte chemotaxins and because of the recent demonstration that slow reacting substance of anaphylaxis (SRS-A) is a leukotriene (78-80). While fewer data are available relevant to the pathophysiologic importance of lipoxygenase products, several lines of evidence suggest the importance of this pathway in mediating lung injury in ARDS. First, if granulocytes are important, there are obvious potential

interactions between lipoxygenase products and granulocytes. Second, recent studies have suggested that lipoxygenase products may be involved in mediating the late phase capillary permeability changes seen following endotoxemia. Increases in one of the products of the lipoxygenase pathway, 5-hydroxyeicosatetraenoic acid (5-HETE), following endotoxemia infusion in sheep has been found. The increase in concentrations of 5-HETE occurs later than the peak concentration of thromboxane and coincides with period of maximal leukopenia. The increase just precedes the apparent increase in lung vascular permeability (81).

Cellular-arachidonate Interaction in Lung Injury

While it should be viewed as pure speculation, the temptation to present a unifying hypothesis to explain the acute vasular injury is irresistible. Such a hypothesis is diagramed in Figure 10. Granulocytes are activated, perhaps by complement, with the resultant production of lipoxygenase products of arachidonic acid. These products are capable of activating granulocytes, thus establishing a positive feedback granulocyte activation loop (82).

Figure 10



Additionally, lipoxygenase products such as SRS-A, may cause airway responses and may also participate in increased lung vascular permeability (83). Activated granulocytes may adhere to one another in the lung microcirculation where generation of superoxide and other free radicals results in capillary injury. Cylo-oxygenase products of arachidonate may be produced by activated granulocytes or perhaps more likely from platelets. Thromboxane A_2 is a potent smooth muscle constrictor and might result in vasoconstriction and airway constriction. In addition, prostacyclin, a dilator prostaglandin, might be responsible for mediating loss of hypoxic vasoconstriction contributing to intrapulmonary shunting and hypoxemia.

It should be re-emphasized that this pathogenetic scheme is largely hypothetical and much more information is required to validate this scheme. It is entirely possible, perhaps even likely, that other humoral mediators, platelets and perhaps even other cellular mediators (for example, mast cells or lymphocytes) participate in the pathogenic sequence of events in ARDS. Clearly, specific delineation of the mechanisms of acute lung injury in this syndrome must await further research.

REPARATIVE RESPONSE TO LUNG INJURY: RAPID EXTENSIVE PULMONARY FIBROSIS

Histologic data obtained from the study of extra-corporeal membrane oxygenation alerted investigators to the devastating rapidity of progression of ARDS. This study revealed that one of the most striking features of ARDS was the presence of an inflammatory response that could transform a previously normal lung into a diffusely fibrotic lung incapable of sustaining life within 3 weeks. The fibrotic process appeared rapidly and progressively obliterated alveoli, alveolar ducts, and the pulmonary interstitium. It appeared to be the principal cause of death in most of the patients in the ECMO studies (28). Increased collagen content in the lungs of all patients who survived for more than 12 days has been demonstrated by measuring the hydroxyproline content of postmortem lung specimens (84). These observations suggest that preventing the acute pulmonary fibrosis is essential to improving survival in ARDS.

Virtually nothing is known of the intermediate messages that link the capillary-leak syndrome, and the maladaptive fibrotic response in ARDS. However, similarities with other fibrotic disorders suggest several possibilities. Idiopathic pulmonary fibrosis and ARDS are similar in several respects (30). Both show morphologic evidence of an acute alveolitis characterized by edema, alveolar and interstitial inflammatory infiltrates, and hemorrhage which are followed by a proliferative phase, followed in turn by alterations in alveolar architecture and the appearance of interstitial fibrosis. In animal models of pulmonary fibrosis this occurs within two weeks paralleling the chronology of evolution of ARDS. Both ARDS and idiopathic pulmonary fibrosis are characterized by a neutrophilic alveolitis and by alveolar lavage fluid containing leukocyte proteases (61, 85, 86). The complement system has been linked to both the acute alveolitis of idiopathic pulmonary fibrosis and to the acute injury of ARDS (87). Cultured fibroblasts from patients with idiopathic pulmonary fibrosis and from animals with pulmonary fibrosis induced by acute lung injury show altered patterns of collagen synthesis producing increased ratios of type I to type III collagen as compared with fibroblasts from normal controls (88, 89). Thus, the disordered architectural arrangement of collagen fibers which occurs in both idiopathic pulmonary fibrosis and in ARDS may share a mechanism of injury and may differ largely in the relative

amount of lung injury that is undergoing the sequence of injury and repair. Idiopathic pulmonary fibrosis might well be a disease characterized by on-going cumulative injury and repair over months or years while ARDS is characterized by massive acute injury and rapid extensive pulmonary fibrosis.

While the mechanisms of the disordered fibrotic response are unknown, considerable recent clinical and experimental evidence suggest that certain standard therapeutic interventions utilized in ARDS may worsen previous lung damage and promote the fibrotic response.

Effect of Oxygen Therapy on Lung Injury and Repair

Within just a short time after the discovery of oxygen 200 years ago, Joseph Priestley, one of its co-discoverers was already cautioning that oxygen "might burn the candle of life too quickly and too soon exhaust the animal powers within" (90). Priestley's prescient speculations about the toxic nature of excess oxygen have been confirmed by a host of succeeding investigators. Recent clinical observations suggest that oxygen may worsen previous lung damage when it is given in a lower concentration than that previously thought to be harmful. Review of pathological materials from the study of extracorporeal membrane oxygenation revealed that the degree of pulmonary fibrosis in patients treated with conventional therapy or with membrane oxygenation was better correlated with the duration of respiratory support that the patient received than with the duration of their illness (28). The histologic pattern seen in these patients mimicked that of oxygen toxicity possibly implicating oxygen in the lung injury and in the fibrogenesis, even though efforts were made during therapy to minimize inspired oxygen concentrations. Much new basic information of potential clinical importance regarding the probable mechanism of oxygen toxicity and the biochemical and morphological responses of lungs to oxygen challenge have been reported recently. A brief review of this basic research data will be presented as a prelude to evaluating the role of oxygen therapy in inducing lung injury and fibrosis in ARDS.

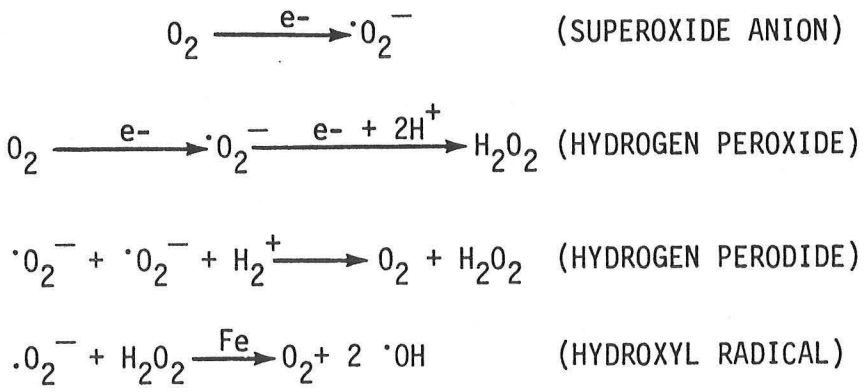
Biochemistry of Oxygen Toxicity: Oxygen is used by the tissues in a variety of biochemical processes with different end products under normoxic conditions. Most of the molecular oxygen is reduced by mitochondrial cytochrome oxidase in a four electron reduction with water as the end product (91).

$$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$$

Other enzymatic reactions add electrons to oxygen one at a time. This univalent pathway involves the production of intermediate compounds or "free radicals" which are thought to be the agents responsible for the cellular damage associated with oxygen toxicity (91-95). The oxygen intermediates produced by single electron transfers are shown in Figure 11. The addition of one electron to molecular oxygen produces the superoxide ion. This molecule is very reactive and can function as an oxidant by obtaining an electron from another molecule or as a reductant by giving up its unpaired electron and being oxidized back to molecular oxygen. The addition of a second electron to the superoxide anion produces hydrogen peroxide, (H_2O_2), a compound that is toxic to intracellular structures even in small concentrations. Two superoxide anions can also react with each other directly to form H_2O_2. Once H_2O_2 has been formed, it can then react with a single superoxide anion to form the hydroxyl radical.

Figure 11

OXYGEN INTERMEDIATES

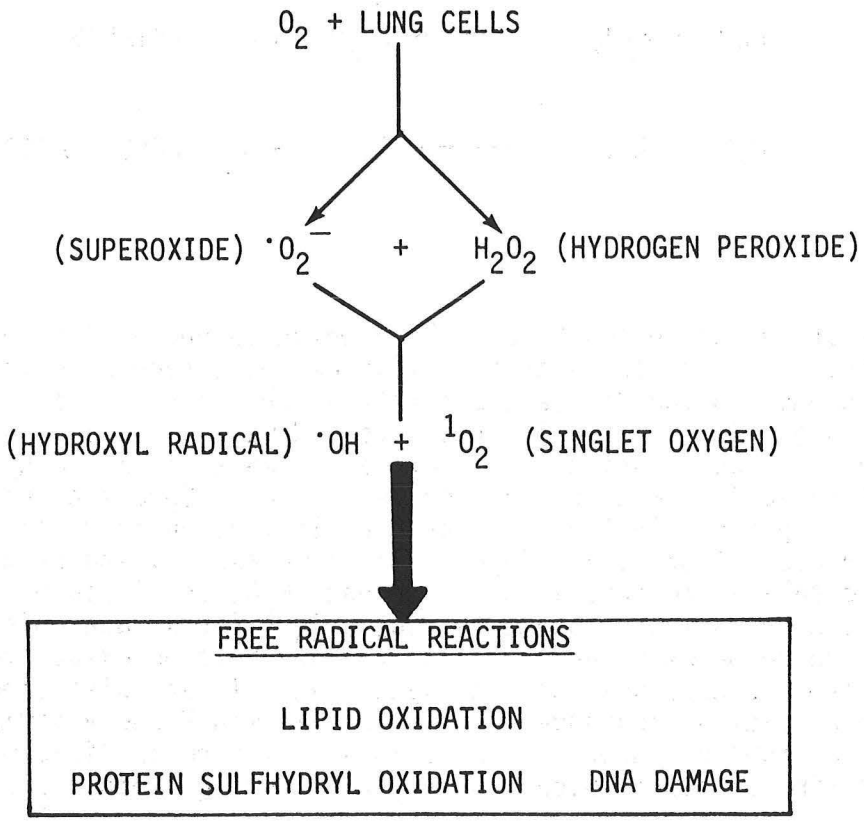


This molecule is one of the most reactive species known to organic chemistry and will damage almost every molecule found in living cells. Also produced during the breakdown of superoxide radicals is excited state oxygen or "singlet oxygen". This product can oxidize many different molecules and causes damage to cellular membranes. While the superoxide anion has received a great deal of attention, some investigators feel that the most destructive property of the superoxide anion is its ability to form the hydroxyl radical and singlet oxygen (96).

The currently popular theory of the chemical mechanism of oxygen toxicity is that specific cell damage is caused primarily by the production of oxygen radicals or other chemically active oxygen metabolites (97, 98) (Figure 12).

Figure 12

Mechanisms of Oxygen Toxicity



Once oxygen intermediates are formed in large amounts (such as the situation which occurs with hyperoxia) a number of destructive chain reactions can occur that lead to cellular death. Free radicals attack the polyunsaturated fatty acid side chains of membrane lipids to initiate the process of lipid peroxidation. These lipid peroxides are powerful inhibitors of many cellular enzymes and can also decompose to yield products that are damaging to proteins in membranes. Oxygen radicals also cause direct nucleic acid damage and protein sulfhydryl oxidation which leads to intracellular enzyme inactivation (99-104).

Figure 13

ENZYMATIC DEFENSES

$$O_2^- + O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2 \qquad \text{SUPEROXIDE DISMUTASES}$$

$$H_2O_2 + H_2O_2 \longrightarrow 2H_2O + O_2 \qquad \text{CATALASES}$$

$$H_2O_2 + RH_2 \longrightarrow 2H_2O + R \qquad \text{PEROXIDASES}$$

Protective mechanisms have evolved which defend against oxygen radical damage. These include cellular oxidative enzymes, such as cytochrome oxidase, that can accomplish the divalent and tetravalent reduction of oxygen without releasing large numbers of these radicals. However, small numbers of free radicals are released during normal oxidative metabolism and hyperoxia produces a rapid increase in their concentration. Specific enzymatic defenses are therefore present in the cell for the elimination of these radicals once they are formed (Figure 13). Superoxide dismutase eliminates the superoxide anion and catalase and peroxidases eliminate H_2O_2 and lipid peroxides. The most important peroxidase enzyme is glutathione peroxidase which directly reduces hydrogen peroxide and can also reduce lipid peroxides to hydroxyacids (105). Enzymatic defenses against oxygen radicals are also aided by non-specific free radical scavengers including vitamin E and vitamin C. These compounds can donate hydrogen to peroxides that form in lipid membranes and stop the chain reactions which are occurring during lipid peroxidation (106).

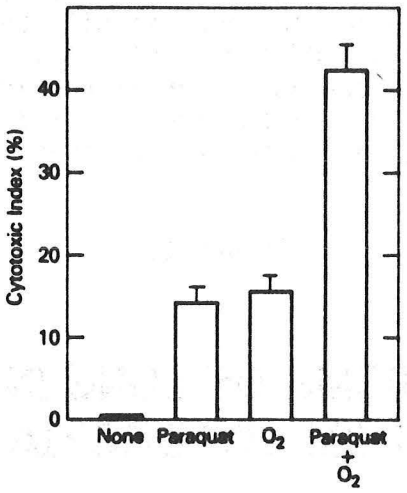
Oxygen Induced Lung Injury: Oxygen may contribute to the lung injury in ARDS in three specific ways: A) by directly injuring lung cells; B) by the recruitment of blood-borne inflammatory and immune effector cells; and C) by promoting fibrosis in the injured lung. Each of these will be discussed briefly.

Evidence supporting the possibility that oxygen radicals can directly damage the lungs comes from a number of sources. Martin, et al., have recently reported studies in which an *in vitro* cytotoxicity assay was used to quantify the ability of hyperoxia to directly injure lung parenchymal cells (107). The assay utilized freshly explanted ^{51}Cr-labeled lung tissue as the target and allowed them to assess the effects of hyperoxia in an environment where indirect mechanisms such as recruitment of inflammatory cells were not

possible. As shown in Figure 14, human lung parenchymal cells were susceptible to oxidant injury. Both oxygen and paraquat can directly injure the cells of the lower respiratory tract without enlisting the aid of blood derived inflammatory cells. Additionally, as shown in Table 8, oxygen radical inhibitors, particularly catalase and alpha-tocopherol (vitamin E) reduced hyperoxia and paraquat induced lung injury.

Figure 14

Direct Oxidant Injury to Human Lung Parenchymal Cells



Martin, J. Clin. Invest. 68:1277, 1981

Table 8

Protection Afforded to Human Parenchymal Lung Cells by Antioxidants from the Effects of Paraquat and Hyperoxia

Condition	Cytotoxic Index %
Paraquat + O_2	42.3 ± 3.5
+ SOD	31.4 ± 3.0
+ CAT	18.8 ± 1.7
+ ASC	31.5 ± 3.4
+ αTOC	19.7 ± 2.3

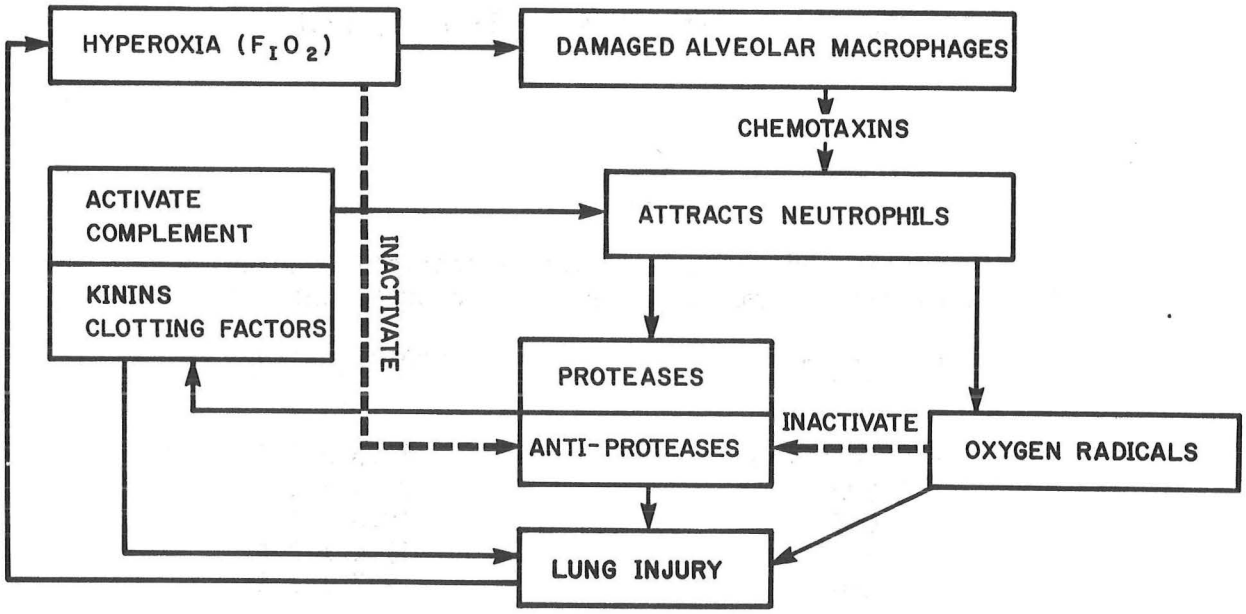
Martin, J. Clin. Invest. 68:1277, 1981

The pattern of protection may provide a clue to the site of cellular injury. Catalase is a large macromolecule and likely remains extracellular in this explant system. Vitamin E was also protective. Being lipid soluble, vitamin E might have access to the lipid layer of the cell membrane, protect unsaturated double bonds within cell membrane lipids, and thus help to maintain the integrity of the cells. Consequently, because one agent that is effective in reducing the oxidant injury is primary extracellular (catalase) and another agent presumably can be intracellular (vitamin E), it is likely that the critical cytotoxic lesion these agents are reducing resides at the cell membrane.

As outlined earlier, recruitment of neutrophils to the lungs may be important in inducing the acute vascular injury. While intravascular generation of C5 fragments in experimental animals produces transient accumulations of neutrophils in the lungs, only minimal amounts of lung edema occur. Indeed, an additional insult may be needed to cause significant edema in C5a models of ARDS (108). It is possible that additional stimuli, generating additional chemotaxins, are needed to produce ARDS. An attractive source of additional chemotoxin is the strategically located alveolar macrophage. Recent studies have provided support for the mechanism of lung injury shown in Figure 15.

Figure 15

MECHANISMS OF LUNG INJURY FROM HYPEROXIA

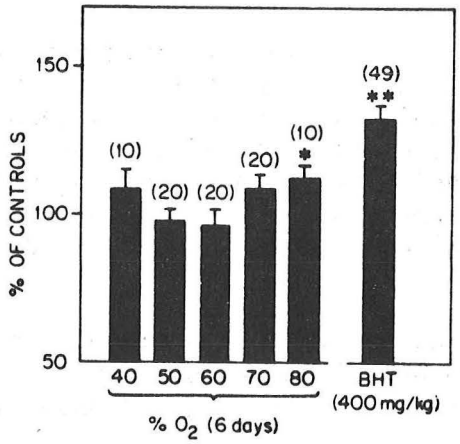


It is known that alveolar macrophages can make chemotoxins for neutrophils (109-112). Additionally, hyperoxia has been shown to stimulate alveolar macrophage release of chemotoxins which attract neutrophils to the alveolar spaces (113, 114). Hyperoxia also causes the release of factors which stimulate neutrophils to produce oxygen radicals and proteases (115). It is postulated that a portion of the lung injury seen in ARDS is related to these hyperoxia recruited neutrophils and their secreted oxygen radicals. Oxygen may increase existing lung injury in several other subtle ways. As outlined earlier, oxygen can contribute to the deactivation of antiprotease defense mechanisms (63, 64, 116). The inactivation of antiproteases such as α1-PI in the microenvironment of the lungs would allow leukocytic proteases to more readily attack adjacent connective tissue structures. Additionally, this unopposed protease activity might also contribute to further activation of complement which would provide a positive amplification loop for the recruitment of additional granulocytes. Unopposed protease activity might also be important in the activation of clotting factors and the kinin system, both of which could contribute to further lung injury.

Recent experimental studies also support the conclusion that oxygen promotes fibrosis in injured lungs in inspired concentrations that are non-toxic to normal lungs. Witschi, et al., studied the relationship between oxygen administration and lung injury (117). Mice were injected with an anti-oxidant, BHT, which produces lung damage in mice. Following this, the mice were treated with varying concentrations of oxygen for varying lengths of time. Quantitative determinations of lung collagen were made to examine the interaction between BHT and oxygen as shown in Figure 16.

Figure 16

Effects of Oxygen Exposure and Of BHT
On Total Lung Hydroxyproline

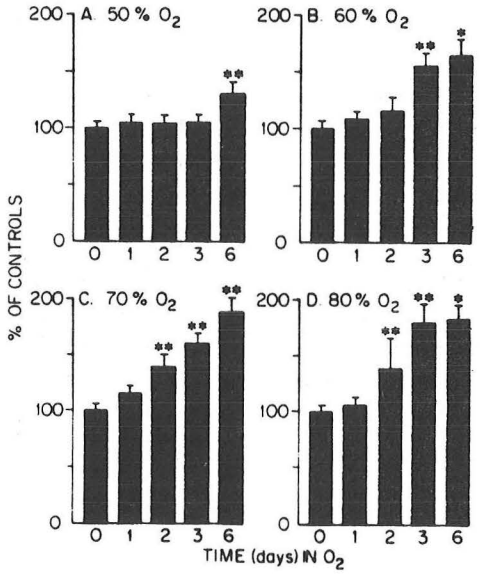


Witschi, Am. Rev. Respir. Dis. 123:98, 1981

Injection of BHT led to a significant increase in total lung collagen. Separate groups of animals were injected with placebo and then exposed to varying concentrations of oxygen for 6 days. Only animals exposed to 80% oxygen for 6 days developed a significant increase in total lung collagen.

Figure 17

Oxygen Exposure: Time and Dose Effects



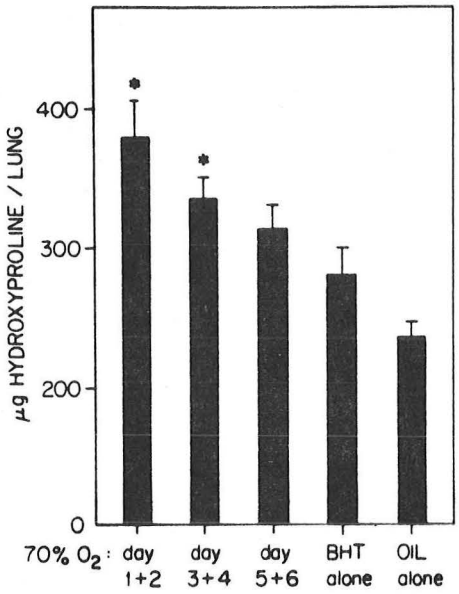
Witschi, Am. Rev. Respir. Dis. 123:98, 1981

However, as shown in Figure 17, exposure to oxygen following injury with BHT further enhanced the development of lung collagen. In BHT treated animals exposed to 50% oxygen, a significant increase was seen after 6 days. Following 60% O_2, the increase was noted after 3 days. Two days of exposure to 70% O_2 was enough to significantly increase lung collagen and 3 to 6 days of exposure enhanced development of fibrosis. Two and 3 days of exposure increased lung collagen following 80% O_2 and resulted in a 60% mortality after 4 days.

Administration of 70% oxygen for 6 days immediately after the initial injury produced fibrosis in animals given doses of BHT that had previously been demonstrated to have no effect on lung hydroxyproline.

Figure 18

Effects of Delayed Oxygen Exposure



Witschi, Am. Rev. Respir. Dis. 123:98, 1981

Fibrosis was synergistic only if oxygen exposure was timed to suppress the burst of DNA synthetic activity that normally follows injury to the lung. As shown in Figure 18, the highest concentration of lung collagen was found in animals that were placed in 70% oxygen for 48 hours immediately after receiving BHT. The response was not as severe when animals were placed in oxygen 2 days after BHT injection. If the animals were kept for 4 days in room air after BHT injection before being exposed to oxygen, the response was even more mild. Since the burst of DNA synthetic activity is believed to represent alveolar type II cell proliferation, this study suggests that oxygen toxicity to a selected subpopulation of lung cells, the regenerating type II cell, might be an important part of ARDS.

This study suggests that administration of oxygen in higher than ambient pressures may establish a vicious circle. The hypoxemia associated with the initial injury makes it necessary to treat the condition aggressively with oxygen. Unfortunately, such supportive therapy may aggrevate the initial lung injury leading to further increases in F_IO_2 and ever increasing lung injury.

Oxygen toxicity has been shown to be augmented by several pharmacologic agents, some of which are in clinical use. Bleomyocin, disulfiram and nitrofurantoin have all been shown to augment oxygen toxicity (118-120). Aminophylline and indomethacin have recently been shown not to induce alteration in oxygen-induced lung toxicity, but the effects of most antibiotics, vasoactive infusions, and other drugs that are given to patients before and during therapy

for ARDS have not been investigated for toxic synergism with oxygen (121). Conceivably, such unsuspecting interactions could partly account for ongoing lung injury in ARDS.

TREATMENT: CLINICAL OPTIMISM OR DESPAIR?

ARDS is an entity that pulmonary physicians treat with increasing frequency. In 1972, a task force from the National Heart and Lung Institute most likely under-estimated the incidence of ARDS at 150,000 cases per year (122). The overall mortality rate of this illness is also difficult to precisely define. Petty, et al., evaluated the outcome of ARDS in 100 consecutive cases and reported a mortality of 66% (14). Of the eight major etiologic factors, sepsis and shock were clearly associated with a poor prognosis. This finding has been confirmed by Kaplan and associates who found that ARDS associated with Gram-negative sepsis had a mortality rate of 90% (123).

The mortality rate of patients with ARDS is also related to the PaO_2 on 100% oxygen as well as to the response of the patients to positive end-expired pressure (21). In a study by Lamy and colleagues, patients on a F_IO_2 of 1.0 who responded to PEEP with a PaO_2 of 150 mm Hg or greater had a mortality of 52%, but patients who responded with a PaO_2 of less than 70 mm Hg had a mortality of 80%. The NIH multicenter study on extracorporeal membrane oxygenation required a PaO_2 of less than 50 mm Hg with an F_IO_2 of 0.6 or greater and reported a mortality of 90% (124). On an even more pessimistic note, the mortality was 61% in all patients age 12 to 65 requiring intubation and ventilation with 50% oxygen for 24 hours (27). When all causes of ARDS are included it is likely that the overall mortality is 60%.

At present, despite advances in our understanding of the pathophysiology of ARDS, most of our therapeutic maneuvers are based on empiric observations rather than on a true understanding of the mechanisms involved in the initial lung injury. Further, the mechanisms involved in preventing lung injury or augmenting the reparitive process are largely unknown. Three broad areas of therapy will be considered in this section: A) oxygen administration; B) mechanical ventilation; and C) the use of corticosteroids.

Oxygen Administration

The air which nature has provided for us is as good as we deserve.
Joseph Priestley, 1775

All patients with ARDS require oxygen. The critical question is, how much oxygen can one give a patient with ARDS without doing more harm than good? This perplexing question must be answered in the management of every acutely ill hypoxemic patient. While data are limited, attempts have been made to gain information about symptomatic, physiologic, and anatomic alterations in the lungs of persons exposed to high concentrations of oxygen.

Normal volunteers exposed to 100% oxygen become symptomatic with substernal pain and mild dyspnea 6 to 24 hours following exposure (125, 126). However, Van De Water, et al., showed that 6 to 12 hours of 100% oxygen at sea level in normal subjects failed to produce any changes in the alveolar arterial oxygen gradient, pulmonary artery pressure, total pulmonary vascular resistance, cardiac output, or pulmonary extra-vascular water volume. In addition subjects

were asymptomatic and there was no change in the chest x-ray (127). Similarly, Singer, et al., found that patients post cardiac surgery exposed to 100% oxygen for 21 to 44 hours had no detectable physiological alterations (128).

However other investigators have presented conflicting evidence on physiologic alterations in subject exposed to high oxygen concentrations for varying time intervals. Comroe, et al., found a decrease in vital capacity in normal subjects exposed to 100% oxygen for 24 hours at sea level (129). Small decreases in static and dynamic compliance and in diffusing capacity as well as increases in wasted ventilation and in arteriovenous shunting have all been described following inhalation of 100% oxygen at sea level for periods up to 48 hours (130-132). If exposure to 100% oxygen continues until the patient withdraws, normal voluntary tolerance last for approximately 72 hours, with the longest recorded exposure being 110 hours. After prolonged exposure periods, the subjects all showed severe pulmonary dysfunction and were markedly symptomatic with dyspnea (133).

Exposure of normals to oxygen concentrations less than 100% decreases the severity of pulmonary symptoms. Space physiologists have shown that normal man can withstand the equivalent of 55% inspired oxygen for 1 week with substernal discomfort. No significant changes in vital capacity occurred (134). Similar experiments have shown that normals can withstand the equivalent of 35% inspired oxygen for as long as 30 days without symptomatology or pulmonary dysfunction (135).

Finally, evidence exists that long-term exposure to oxygen even at inspired concentrations of 24 to 28% causes mild damage. Petty found proliferative and fibrotic changes in 6 of 12 autopsy cases in patients receiving long term home oxygen (136).

Most of the data reviewed in this section concerning the safety or toxicity of administering elevated inspired oxygen concentrations have been collected from exposures involving normal subjects. Patients with pre-existing pulmonary diseases may have an altered response to hyperoxia which could result in either an increased sensitivity or an increased tolerance to oxidant lung damage. The effects of the pharmacologic or mechanical therapies that are administered simultaneously with oxygen therapy to patients with acute respiratory failure are unknown.

Evaluation of the data obtained from normal human exposures allows the following conclusions:

1. Exposure to 100% oxygen for up to 24 hours is associated with an early tracheitis, but there has been no identifiable clinically significant abnormality.
2. Exposure to 55% oxygen for a period of days to weeks causes early symptoms of toxicity, but no measurable changes in pulmonary function or arterial blood gases, while exposure to 35% oxygen for the same period is well tolerated. Because of these findings, it is reasonable to believe that human tolerance for oxygen for any protracted period lies between these two values. On the basis of this information, patients with acute respiratory distress often receive inspired concentrations of oxygen up to 50 to 60% before other therapeutic measures to prevent hypoxemia are instituted.

3. Inspired oxygen delivered at concentrations between 55 and 100% carries a risk of lung damage. The duration required to produce damage seems to be inversely proportional to the concentration of inspired oxygen. The onset of oxidant lung injury is impossible to determine and is most likely variable. Because of the difficulty in determining the onset of toxicity it is recommended that the lowest possible oxygen concentration that maintains tissue oxygenation be administered.

4. If reduction in the inspired oxygen concentration to less than 55% produces unacceptable arterial hypoxemia (an arterial oxygen saturation of less than 90%) other therapeutic measures must be instituted. The use of continuous positive pressure ventilation allows the recruitment and improved ventilation of gas exchange units and thus the reversal of intrapulmonary shunting (23). With improved gas exchange, the inspired oxygen concentration required to maintain adequate tissue oxygenation can be reduced and the risk of oxygen toxicity decreased. Therapeutic agents which increase cardiac output, or the administration of red blood cells to anemic patients may also improve tissue oxygenation and decrease the need for high inspired oxygen concentration.

Mechanical Ventilation

Mechanical ventilatory support is essential in most patients with ARDS. The decision to perform endotracheal intubation and ventilatory support may be difficult. Animal studies of ARDS suggest that early ventilatory support decreases morbidity and mortality significantly more than when these modalities are used in well developed lesions (137, 138). Thus, because of the suggestion that early intubation may be beneficial, it is probably better to err on the side of instituting mechanical ventilation too early rather than delaying the decision until severe tissue hypoxia and lung dysfunction have ensued. Guidelines that have been found to be useful are shown in Table 9 (18).

Table 9

Guidelines for Ventilatory Support in Patients With ARDS

Respiratory rate	> 35/minute
PaO_2 on mask O_2	< 70 mm Hg
PAO_2-PaO_2 on 100% O_2	> 450 mm Hg
V_D/V_T	> 0.60

Pontoppidan, N. Engl. J. Med. 287:690, 743, 799, 1972

In order to accomplish mechanical ventilation, an artificial airway is needed. A plastic endotracheal tube with a low-pressure, high-compliance balloon cuff can be maintained in place for 14 days. Vocal cord paralysis, tracheomalacia, stenosis and perforation into the esophagus or great vessels are now relatively uncommon (139). Tubes with an internal diameter of less than 8 mm have significant resistance to airflow and introduction of a suction catheter or fiberoptic bronchoscope is more difficult (140). If possible, a tube larger than 8 mm should be inserted.

Volume-cycled ventilators are the accepted choice for long-term ventilatory support in respiratory failure. A volume-cycled ventilator will provide a prescribed tidal volume in spite of moderate changes in compliance or resistance. It makes little difference whether ventilator output is a square wave or sine wave. Tidal volumes of 10 to 15 ml/kg of body weight are usually required to provide adequate ventilation for the non-compliant lungs of ARDS, although the actual value is limited by resulting peak airway pressures and potential barotrauma. High tidal volumes reduce the likelihood of atelectasis of terminal air spaces, but it remains common practice to use a prophylactic mechanical sigh about every 100 breaths with a volume of approximately 50% of the patient's predicted vital capacity. Arterial carbon dioxide tension reflects adequacy of alveolar ventilation and should be maintained at a level slightly below the normal value of 40 mm Hg.

The relationship of $PaCO_2$ to alveolar ventilation is linear, but this is not true for PaO_2 and consequently adequate ventilation is not synonymous with adequate oxygenation. Hypoxemia may persist despite satisfactory alveolar ventilation and a high F_IO_2. As previously indicated, positive end-expiratory pressure (PEEP) is commonly employed to combat hypoxemia. Although PEEP will increase the PaO_2 in the majority of patients, the mechanism whereby this occurs is still uncertain. Introduction of end-expiratory pressure of 5 to 15 cm H_2O increases functional residual capacity and improves arterial oxygenation by inflating non-ventilating units. The subsequent reduction in shunt fraction allows ventilation at lower inspired oxygen concentrations (17). Reducing the F_IO_2 may prevent or delay oxygen induced pulmonary damage. PEEP does not decrease lung water (141).

The use of PEEP is neither universally nor uniformly helpful. Even with an increase in PaO_2, PEEP has potentially deleterious effects on the delivery of oxygen to tissues. Although the effect of PEEP on the cardiac output in a given patient is unpredictable, most studies record some reduction in output (142). Since oxygen delivery depends on cardiac output as well as on the oxygen content of arterial blood, a satisfactory balance must be reached (142-143).

Whether PEEP actually improves survival rates has recently been questioned. Springer, et al., retrospectively reviewed 78 patients whose arterial oxygen tension was less than 70 mm Hg despite a F_IO_2 of 1.0 (144). Sixty percent of these patients were ventilated with PEEP. There was no difference in clinical illnesses or severity of cardiopulmonary dysfunction from the patients ventilated without PEEP. PEEP increased the mean survival from 4.2 to 9.2 days but overall survival was similar at 31% with and 26% without PEEP. An improvement in PaO_2 and a decrease in shunt fraction following a trial of PEEP predicted a favorable outcome, but its continued use appeared to prolong life

for a few days without affecting hospital mortality. It should be noted that this study included patients with all forms of acute respiratory failure, without attempts to select patients with well-defined ARDS. At the present time there is no evidence to suggest that PEEP is indicated except in patients requiring potentially toxic concentrations of inspired oxygen to maintain adequate arterial oxygenation. While these finding should not be interpreted as precluding the potential usefulness of PEEP in certain situations, they do point out the need for prospective studies designed to document the type of patients for whom PEEP would be beneficial rather than harmful or useless.

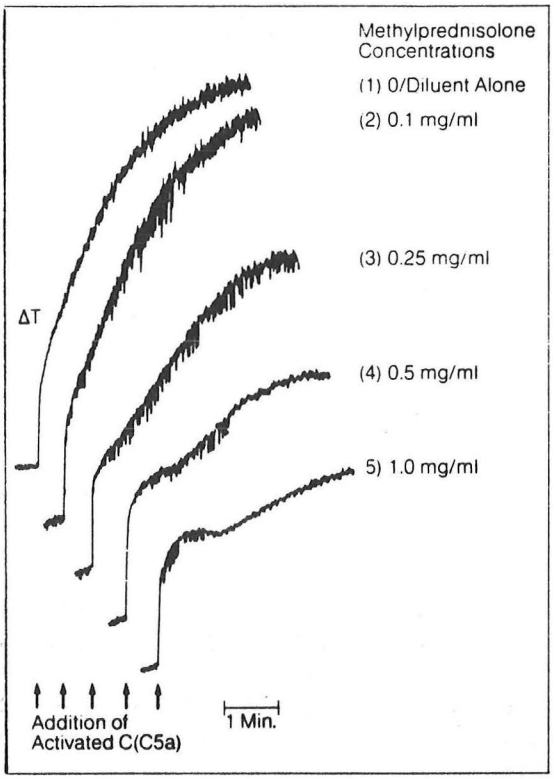
Corticosteroids In Adult Respiratory Distress Syndrome

Corticosteroids offer several theoretical advantages in treating the adult respiratory distress syndrome including their presumed ability to affect inflammation, intravascular coagulation, pulmonary blood flow, alveolar epithelial cell function and the evolution of inflammation to pulmonary fibrosis. In spite of these theoretical advantages, controversy surrounds the use of high dose corticosteroid therapy in ARDS. This is a topic of considerable debate with an extensive and diverse literature, but an attempt will be made to review the experimental and clinical evidence in order to answer two clinically relevant questions: A) Is there theoretical and experimental justification for massive steroid therapy, and B) Is there acceptable evidence of clinical benefit?

Experimental Studies: Complement induced granulocyte aggregation may be involved in the initial vascular injury in ARDS. *In vitro* data suggests that very high levels of corticosteroids inhibit complement induced granulocyte aggregation and thereby reduce the propensity of these cells for leuko-embolization to the lung (145). When methylprednisolone was added to granulocytes in an aggregometer, a dose-dependent inhibition of complement induced granulocyte aggregation could be demonstrated as shown in Figure 19. At levels of 1 mg/ml, a dose roughly equal to that present in plasma after the administration of 30 mg/kg of methylprednisolone, the aggregation response was virtually prevented. Similar concentrations also significantly suppressed damage to cultured endothelial cells provoked by activated complement and granulocytes. These studies suggest that corticosteroids may ameliorate two pathological characteristics of shock lung, microvascular plugging by granulocytes and pulmonary endothelial damage.

Figure 19

Inhibition of Pulmonary Leukostasis and Endothelial Damage by Glucocorticosteroids in Septic Shock*



Supporting evidence suggesting a beneficial effect from corticosteroid therapy comes from studies of lung vascular permeability following infusions of endotoxin (146). Infusions of *E. coli* endotoxin cause an initial period of pulmonary hypertension followed several hours later by long periods of increased vascular permeability. During the later stages, lung lymph flow is markedly increased. When high doses of methylprednisolone (in the range suggested for use in humans with septic shock) were administered 30 minutes

prior to infusion of endotoxin, the initial pulmonary artery pressure was less and the increase in lung vascular permeability was prevented (Table 10).

Table 10

Effects of Steroids on Endotoxin Induced Lung Injury

Condition	Mean Pulmonary Artery Pressure ($cm\ H_2O$)	Lung Lymph Flow ml/hr
Endotoxin alone		
Base line	21 ± 1	7.2 ± 0.2
Phase I	53 ± 3	45.4 ± 2.8
Phase II	20 ± 3	23.2 ± 1.0
Endotoxin + steroids		
Base line	21 ± 1	7.6 ± 0.4
Phase I	43 ± 4	26.2 ± 3.1
Phase II	24 ± 1	10.0 ± 0.4

Brigham, J. Clin. Invest. 67:1103, 1981

Methylprednisolone begun during the initial pulmonary hypertensive response to endotoxin also prevented the late phase increase in lung vascular permeablilty, but the drug had no effect once the vascular permeability was increased. These studies suggest that steroids given early in the course of sepsis may help prevent the particularly devastating changes in capillary permeability that occur with this disease.

In addition to these studies there is an immense literature on the use of corticosteroids in experimental models of hemorrhagic and septic shock. The extent of this literature precludes a detailed analysis in this presentation. Twenty-four of the more relevant studies are referenced in the bibliography (147-170). Several problems exist with this group of studies. Random allocation of animals to control and treated groups is mentioned in three studies, but in only one are adequate details provided (148, 153, 170). In no instance were the experiments conducted in a "blind" fashion. Few of the listed experimental studies focus on the development of pulmonary abnormalities. The parameters evaluated in these studies were hemodynamic, biochemical, or gross survival. With these disclaimers in mind, the following conclusions may be drawn from these studies:

1. Corticosteroids produced no consistent effect on mean arterial blood pressure, cardiac output, or peripheral vascular resistance. It is unlikely then, that any putative beneficial effect of corticosteroids in shock derives from inotropism or vasodilation.
2. No consistent effect of corticosteroids was noted on lysosomal enzyme release or on lactate production.

3. The majority of studies revealed improved animal survival, provided corticosteroids were given in high doses near the time of the challenge. This beneficial effect applied more to those studies employing septic shock than hemorrhagic shock. The beneficial effect is lost if the dose is given more than 3 to 4 hours before or after the challenge.

Clinical Studies of Corticosteroids: If animal studies of corticosteroids in ARDS have their weaknesses, clinical studies are beset by a lack of diagnostic criteria, control, and design. Obviously, the disorders that are associated with ARDS are many and these disorders do not necessarily share a common denominator. Of the many disorders associated with ARDS, the use of high dose corticosteroid therapy has been advocated clinically only in hypovolemic and septic shock, fat embolism, acid aspiration, and fresh water near-drowning. From this review, there is sparse clinical evidence of benefit in the latter two situations (171-173). With this in mind, it remains for us to evaluate if there is any factual clinical evidence for the use of corticosteroids in hypovolemic and septic shock.

In a comprehensive review, Weitzman and Berger challenged the therapeutic efficacy of steroids by underscoring the flaws of previous studies of septic shock done in humans. These authors evaluated 32 studies of corticosteroid therapy for bacterial infection for adherence to 8 accepted standards of clinical trial design. Only 44% used a concurrent control population; 41% were prospective experimental trials; but only 16% used a double blind technique and 25% allocated treatment in a random manner. Only 59% of the studies adequately described criteria for diagnosis of the illness treated. The presence of underlying disease was tabulated in 38% and the clinical extent of disease was considered in only 44%. Possible complications of steroid administration were sought in only 38% of studies. This analysis points out that much of the controversy involving the therapeutic use of corticosteroids is perpetuated by studies that are unsatisfying in their use of clinical trial design (174).

While drawing conclusions from faulty data is best described as foolish, certain observations can be made from these studies. I have condensed the authors interpretation of their own results into the terms "beneficial", "harmful, or "no effect". Of 32 reports, 22 considered corticosteroids to favorably influence the course of patients with bacterial infection; 2 considered corticosteroids harmful; and 8 observed no difference between treatment and control groups. If an attempt is made to correlate therapeutic conclusions with adherence to methodologic standards, certain observations can be made. In general, papers advocating corticosteroid therapy were more delinquent in fulfilling principals of clinical trial design than those that did not. In particular, more deficiencies in the use of random allocation and double-blind procedures were found in studies considering corticosteroids beneficial. Finally, in papers on septic shock there were more shortcomings with the respect to the 8 methodologic criteria among studies advocating corticosteroid therapy than those that did not.

Six clinical studies have been published since 1971 (175-180). If these studies are evaluated by the same 8 criteria, they adhere to an average of 3 of the 8 criteria stated above, with only 1 study satisfying 6 of the 8 criteria.

This study, performed by Schumer provides the strongest argument for use of therapeutic corticosteroids (177).

Before reviewing this study, I would like to contrast it to a prospective study of 113 with septic shock treated in the intensive therapy unit of the Western Infirmary in Glasgow (181). Corticosteroids were not used in this study, and thus this study will serve to illustrate the expected mortality in post-operative septic shock following intensive and aggressive therapy without the use of steroids. In this series, mortality from surgical septic shock fell from 71% to 47% over a three year period. The authors ascribe this improvement to the earlier use of cardio-respiratory support, aggressive surgical intervention and more effective use of antibiotics. This study demonstrates that without the use of corticosteroids, a mortality of somewhat less than 50% should be obtainable in post-operative septic shock.

Schumer studied 172 patients with bacteremic septic shock consecutively admitted from the surgical service of the Veterans Administration Hospital between 1967 and 1975 (177). The control group received 100 ml of saline and the treated group either 3 mg/kg of dexamethasone or 30 mg/kg of methyl-prednisolone in 100 ml of saline intravenously, given at the time of diagnosis. If necessary the dose was repeated after 4 hours, but the indications for a repeated dose are not given. The results of this study are shown in Table 11. Thirty-three of 86 saline control treated patients died for a mortality of 38%, and 9 of 86 patients died in the steroid group for a mortality of 11%. It should be noted that mortality in the saline treated group is similar to the mortality achieved in the Glasgow series where corticosteroids were not used.

Table 11

Effect of Steroids in Postoperative Shock

Study	Recovered	Died	Total
Prospective:			
Steroid	77	9 (10.4%)	86
Saline	53	33 (38.4%)	86
			172

Schumer, Ann. Surg. 184:333, 1976

This prospective study has been criticized on several counts: A) use of 2 different steroid preparations; B) failure to use a uniform antimicrobial protocol; C) lack of information about adjunctive supportive therapy; D) deaths associated with septic shock recorded up to 4 weeks and E) unusually low mortality in the corticosteroid treated group (182). While this study is not perfect, I believe the above critisms are weak. Two steroid preparations were used, but doses were comparable and the number of patients in the two groups were identical. Antimicrobial and adjunctive therapy were not standard

over the entire length of the protocol, but no evidence exists that it was different in the control and treated groups. Deaths were recorded up to 4 weeks, but most deaths were recorded within 7 days. Finally, the unusually low mortality in the steroid treated group is an outcome of the study and of itself cannot be used as a criticism of the study design. At present, this is the only reasonably sound clinical study of sepsis available for review.

None of the previously evaluated clinical studies specifically addressed the issue of corticosteroid treatment in ARDS. Three such studies exist.

Ashbaugh and Petty evaluated 51 patients with sepsis and ARDS and divided their patients into 4 groups. Group 1 did not receive corticosteroids before, during, or after ARDS. Group 2 received the equivalent of 0.3 gram of hydrocortisone for a period of 2 days or longer. Group 3 received less than 0.3 grams of hydrocortisone or its equivalent or received larger does for less than a day, and group 4 received corticosteroids prior to experiencing ARDS (183). Survival was approximately 50% in the first 2 groups, whereas no patients in groups 3 or 4 survived. While there was no evidence corticosteroids improved mortality, it was the authors "clinical impression" that corticosteroids influenced the course of ARDS secondary to fat embolism or aspiration pneumonia.

An additional uncontrolled study of 10 consecutive patients with ARDS who were given methylprednisolone over a 48 hour period of time has been reported (178). Treatment with methylprednisolone (30 mg/kg every 6 hours for 36 hours) was associated with a progressive increase in oxygenation and resolution of pulmonary edema.

Perhaps the most convincing evidence that corticosteroids are of use in certain forms of ARDS comes from the studies of Sibbald, et al., (184). These authors evaluated the effect of pharmacologic doses of methylprednisolone (30 mg/kg) and dexamethasone (4 mg/kg) on alveolo-capillary permeability in humans with Gram-negative sepsis and respiratory failure. This study examined the change in clearance of intravenously administered radiolabeled albumin into bronchoalveolar secretion, before and after corticosteroids administration.

Their results are shown in Table 12.

Table 12

Effect of Corticosteriods on Alveolo-Capillary Permeability in Septic ARDS

	Responders		Nonresponders	
	Before	After	Before	After
Clearance of I-HSA, ml/hr	.28	.096	.233	.215
COP, mm Hg	16.72	16.25	15.96	14.98
PA, mm Hg	28.07	25.0	38.4	36.4
PCWP, mm Hg	11.64	11.57	12.39	11.8
CO, L/min	7.63	8.59	8.45	7.68
$\dot{A}$-a$\dot{D}O_2$, mm Hg	395.5	360.8	431.6	410.0
$\dot{Q}s/\dot{Q}t$, %	25.18	22.09	30.6	27.3
Effective compliance, ml/cm H_2O	24.57	21.58	20.2	24.4
Sputum volume, ml/hr	1.41	1.29	1.04	1.09

Sibbald, Chest 79:133, 1981

In 14 of 19 patients, the IV administration of corticosteroids resulted in a significant decrease in the clearance of radiolabeled albumin from blood to bronchoalveolar secretion when compared with clearance values before corticosteroid administration. The mean clearance in the 6 hours before corticosteroid administration was 0.28 ml/hour and the mean clearance in the 6 hours after giving the corticosteroid was 0.096 ml/hour.

In 5 patients, all of whom received methylprednisolone, there was no significant change in the clearance of radiolabeled albumin after administration of corticosteroids. The mean value before giving the corticosteroid was 0.23 ml/hour compared with the mean value after corticosteroid administration of 0.214 ml/hour. The 5 patients who failed to respond to corticosteroid were judged to be more severely ill than the patients who responded in that their mean intrapulmonary shunt fraction and mean pulmonary artery pressures were higher.

This study suggests that most patients with sepsis have a prompt decrease in pulmonary capillary leakage after a massive dose of corticosteroid. The data further suggest that the earlier the dose of corticosteroid is administered, the more effective it will be in stopping the capillary leak syndrome.

These data are disparate from that presented for the sheep endotoxin model. In the sheep endotoxin model, once lung vascular permeability was increased methylprednisolone had no effect, whereas in the human study, methylprednisolone given during periods of increased permeability returned permeability to normal. Two possible explanations exist for this disparity.

First, the human study may relate more to epithelial than endothelial permeability whereas the sheep data relate only to endothelial permeability. Corticosteroids could affect the two barriers differently. Since the alveolar epithelium is less permeable than the capillary endothelium, the epithelium is the primary barrier to movement of solutes from the vascular spaces into the airways. Secondly, and perhaps more likely, humans may undergo repeated bouts of septicemia so that giving steroids even after respiratory failure occurs may favorably affect responses to subsequent or concurrent endotoxemia.

Recommendations for Corticosteroid Use in ARDS

At the present time, neither clinical or experimental studies provide guidance concerning the indications, contraindications, dose, or duration of corticosteroid treatment in patients with ARDS. Some physicians believe strongly that corticosteroids favorably influence the outcome in patients in whom ARDS is present or developing, whereas others regard the data in support of such therapy as insufficient in view of the potential risk. The Food and Drug Administration recently reviewed the indications for the use of corticosteroids in septic shock, focusing on the package insert for Solu-Medrol. The decision was made to remove septic shock from the insert as an indication for the use of high doses of methylprednisolone. This decision followed a review of clinical evidence of the beneficial effects of such a regimen in patients with septic shock. Firm evidence was obviously deemed not to exist.

The past few years have provided evidence of a different nature. In the past it has been difficult to provide a sound explanation for any possible benefit of corticosteroids which is always good ammunition for a skeptic. The recent appreciation of the potential importance of C5 activation in endothelial damage provided a much needed explanation. This observation coupled with the observation of a rise in circulating C5a prior to the development of ARDS in high-risk subjects is of potential clinical significance. Corticosteroids in massive doses have been shown to prevent the effects of C5 activation if given early. To accomplish this effect clinically, a circulating marker for ARDS to identify those patients who are likely to develop this syndrome will be required. Assays for C5a, or the fibrinogen product, D-antigen, may soon serve this purpose (185).

It is clear that a prospective randomized study is urgently needed in ARDS, but such is not available. In its absence I would make the following recommendation. Data are insufficient to encourage large, repeated doses of corticosteroids as adjunctive treatment for all patients with ARDS. The benefits of steroid therapy seem to outweigh the disadvantages of steroid therapy in certain patients with ARDS particularly those with documented sepsis. Given this situation, physicians would seem to be justified in using corticosteroids in this condition to empirically treat ARDS patients. If this approach is adopted, it is prudent to use IV methylprednisolone in pharmacologic doses, 30 mg/kg body weight as a bolus injection. If no improvement occurs within 4 hours, the dose should be repeated once.

EPILOGUE

Many factors which are free in plasma or associated with blood cells are involved in lung injury and eventually in respiratory failure. Not all factors have been identified, but the complement system, products of arachadonate metabolism, vasoactive humoral agents and granulocytes are probably importantly involved in the acute vascular injury of ARDS. Moreover, the possibility exists that hyperoxia interacts unfavorably with underlying lung injury. The course of repair requires further intensive investigation and may mold future strategies for respiratory support.

The events at the molecular and cellular level contributing to or initiating acute lung injury remain complex, multifactorial and poorly understood. Moreover, the clinical situation in which respiratory failure arises is varied and the need for a systematic approach to discovering the initiating events leading to ARDS is apparent. Some progress has been made in the definition of markers for this illness and these are of potential importance in designing definitive therapeutic trials for such agents as corticosteroids. The present treatment of ARDS is largely symptomatic, relying on techniques such as oxygen therapy and positive pressure ventilation to sustain life during the acute and healing phases of the disease. The use of corticosteroids remains controversial, but it is my judgement that as more is learned about the effects of steroids on complement activation and the chemotactic responses of phagocytes in the lungs, more judicious use of steroid therapy will follow. And thus we have come full circle, and are left with unanswered questions and speculations. For those of you who may feel discomforted, I can only quote Charles Darwin:

> "Many of the views which have been advanced are highly speculative, and some no doubt, will prove erroneous; but I have in every case, given the reasons which have led me to one view rather than to another.... False facts are highly injurous to the progress of science, for they often endure long, but false views; if supported by evidence, do little harm, for everyone takes a salutory pleasure in proving their falseness."

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