REVIEW ARTICLES

Adult respiratory distress syndrome—I. Aetiology and mechanisms

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Introduction

The adult respiratory distress syndrome (ARDS) represents a final common pathway of injury due to a large variety of massive, often unrelated, insults to the lung (Table 1). For example, the injury may be a consequence of direct pulmonary damage such as aspiration of gastric contents or pulmonary contusion or the result of a systemic process such as sepsis or cardiopulmonary bypass. Acute respiratory distress as a consequence of trauma, burns, sepsis and long surgical procedures was described by Moon in 1936. He suggested a direct injury to pulmonary capillary endothelium and plasma extravasation causing pulmonary oedema. More recently, ARDS was described as a distinct clinical entity with many causes (Ashbaugh *et al.*, 1967).

cies are present in both syndromes but are a consequence of diffuse lung injury in ARDS, in contrast to a deficiency as a primary aetiology in the infant respiratory distress syndrome. A debate has raged for several years concerning the appropriateness of the present title ARDS. One camp claims that lumping all of the different causes (Table 1) of ARDS together is crucial as the pathophysiology and management is almost always similar regardless of course. Another group passionately argues that we should split ARDS into specific syndromes for each cause. The latter stresses that future insight into mechanisms may lead to specific differences in treatment. We believe that this argument is moot. Lumping helps to identify the remarkable similarities among patients with ARDS while splitting is impor-

TABLE 1. Aetiology of ARDS

Aspiration of gastric contents	Near-drowning
Cardiopulmonary bypass	Neurogenic
Diffuse pneumonia (viral, bacterial, fungal, mycoplasma, pneumocystis)	O ₂ toxicity
Drug overdose (acetylsalicylic acid, ethchlorvynol, heroin, methadone, propoxyphene)	Pancreatitis
Disseminated intravascular coagulation	Paraquat toxicity
Eclampsia	Pulmonary contusion
Fat embolism	Radiation
High altitude	Sepsis
Idiosyncratic drug reaction	Smoke inhalation
Irritant gas inhalation	Surface burns
Leukaemia	Thrombotic thrombocytopenic purpura
Multiple transfusions	Trauma
	Venous air embolism

ARDS is certainly not new as a clinical entity and has had numerous synonyms over the past five decades (Table 2). The current familiar title was given due to its many apparent pathophysiological similarities to the infant respiratory distress syndrome (Ashbaugh *et al.*, 1967). Surfactant deficiency

to identify subpopulations of patients who might respond to specific therapies in the future.

At present there is no single diagnostic test or marker of ARDS. To confirm a diagnosis of ARDS a clinical description of the syndrome must be used as a definition. Criteria for the diagnosis of ARDS include: (1) clinical history of a pulmonary or non-pulmonary catastrophic event (aspiration, multi-system trauma, sepsis) with respiratory failure;

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TABLE 2. Synonyms for ARDS

Shock lung	Blast lung
Traumatic wet lung	Congestive atelectasis
Da Nang lung	Adult hyaline membrane disease
Pump lung (postcardiopulmonary bypass syndrome)	Stiff lung syndrome
Capillary leak syndrome	Respirator lung
Non-cardiogenic pulmonary oedema	

(2) exclusion of cardiogenic pulmonary oedema or chronic pulmonary disease as the main cause of respiratory failure; (3) clinical respiratory distress with hypoxaemia, tachypnoea and dyspnoea, (4) diffuse pulmonary infiltrates on chest X-ray; and (5) physiological measurements that may include P_{aO_2} less than 50 mmHg when F_{iO_2} is greater than 0.6, reduced respiratory compliance, increased shunt fraction (Q_s/Q_T) and increased deadspace ventilation (V_D/V_T) (Petty and Fowler, 1982). Although the histopathological picture can be used as a diagnostic criterion for ARDS, a biopsy is seldom if ever indicated. It is not necessary to include all of the above criteria to make a diagnosis of ARDS, as these rigid criteria may omit early cases of ARDS. However, it is mandatory to include the first four criteria listed. The pathology is discussed more fully in the body of the text.

ARDS has been recognized as a common and lethal syndrome, killing at least half of an estimated 150,000 afflicted in the United States in 1976 (Lung Program, 1972). Clearly this syndrome is particularly tragic in that many of its victims are young and previously healthy. In fact, ARDS will probably kill more Americans this year than the combined annual mortality from breast and prostate cancer (Silverberg and Lubera, 1983).

Recently, two prospective studies have highlighted the epidemiology of ARDS (Fowler *et al.*, 1983; Pepe *et al.*, 1982). Both groups designed studies to quantitate the incidence of ARDS in patients who fell into high risk categories (Table 1). Fowler and colleagues prospectively identified 936 patients who had one or more of the eight conditions thought to predispose to respiratory failure. These conditions were cardiopulmonary bypass surgery, burn, bacteraemia with clinical signs of infection, hypertransfusion, long bone or pelvic fracture, pneumonia needing intensive care, disseminated intravascular coagulation and pulmonary aspiration. This study showed the incidence of ARDS in patients who fell into the aforementioned categories to be 5.8% in patients who fell into one category and 24.6% in patients who were categorized into two or more of these eight predispositions. A smaller study showed a similar relationship between number of risk factors and incidence of the syndrome (Pepe *et al.*, 1982).

After examining the exhaustive list of predispositions to this syndrome, it seems difficult to imagine a common pathogenic mechanism for ARDS. Within the past few years a virtual explosion of information relevant to ARDS has emerged. In these reviews we will attempt to highlight the major conceptual trends of this work and to integrate the proposed aetiology, mechanisms, pathophysiology and management of patients with this syndrome.

Mechanisms of ARDS

Acute injury to the pulmonary capillary endothelium is an integral aspect in the pathogenesis of ARDS. Many cellular and humoral factors have been implicated as causes of pulmonary capillary endothelial injury (Fig. 1). These include neutrophils, arachidonic acid metabolites, fibrin and fibrin degradation products (FDP), complement, histamine, serotonin, bradykinin, and platelets.

FIG. 1. Mechanisms of pulmonary capillary endothelial damage. There are four major causes of pulmonary capillary endothelial damage. These are neutrophil injury, direct injury, arachidonic acid metabolite injury and coagulation product injury. Other cellular and humoral factors which have been implicated include complement, histamine, serotonin, bradykinin, and platelets.

Attraction of neutrophils

Considerable experimental and clinical evidence has accumulated to implicate neutrophils in the genesis of ARDS (Tate and Repine, 1983; McCord,

1983; Hammerschmidt, 1983; Till *et al.*, 1982; Cochrane *et al.*, 1983b). The data supporting the critical role of neutrophils in the aetiology of pulmonary endothelial damage is convincing. For example, morphological data reveal deposition and aggregation of neutrophils in the pulmonary vasculature in animals with acute lung injury (Shasby *et al.*, 1982; Barle, Tahmont and Malik, 1982; Craddock *et al.*, 1972). Neutrophil depletion studies have been performed in animal models with endotoxaemia, hyperoxia, pancreatitis and microembolization (Barle *et al.*, 1982; Heflin and Brigham, 1981; Flick, Perel and Staub, 1981). Neutropenic animals failed to develop significant capillary leak when confronted with the insults listed above; yet non-neutropenic animals subjected to pancreatitis, endotoxaemia, microembolization and hyperoxia developed significant ARDS. Clinical data is partially based on bronchoalveolar lavage fluid from patients with ARDS. Several investigators have demonstrated neutrophil elastase and neutrophil derived oxidants in the lavage fluid (Tate and Repine, 1982; Fantone *et al.*, 1983; Lee *et al.*, 1981; Cochrane *et al.*, 1983b). Both the release of elastase and the generation of oxidants by neutrophils can lead to severe pulmonary injury (Cochrane, Spragg and Revak, 1983a). Finally, neutrophils obtained from pulmonary artery blood from critically ill patients with ARDS appear to be in a functionally and metabolically activated state compared to critically ill patients without ARDS (Zimmerman, Renzetti and Hill, 1983). These data illustrate that in ARDS neutrophils are present in high concentrations and are in a metabolically active state so they can release proteases and oxygen metabolites that are toxic to the lung.

Clearly, for neutrophil-dependent lung injury to occur, a potent stimulus must exist to promote neutrophil aggregation in the lungs. Many chemoattractants are normally present in the lung to effectively mobilize the neutrophils for an appropriate response to an invading bacteria or foreign body. Yet, in response to the catastrophic events that predispose a patient to ARDS, it appears that many chemoattractants and several substances that injure the endothelium act synergistically to perpetuate lung injury. In many of the most common clinical contexts for the development of ARDS, such as sepsis and severe trauma, the complement cascade is activated (Hammerschmidt *et al.*, 1980). In addition, hyperoxia stimulates alveolar macrophages to release neutrophil chemoattractants that may be important in perpetuating ARDS (Tate and Repine, 1983).

Complement component C5a has been shown to attract and aggregate neutrophils *in vivo* (Craddock *et al.*, 1977). Following an observation of lung dysfunction in haemodialysis patients, Craddock and colleagues infused activated complement into experi-

mental animals and found pulmonary leucostasis and pulmonary dysfunction (Craddock *et al.*, 1977). Also, in a group of patients followed prospectively, elevated C5a was significantly correlated with the development of ARDS (Hammerschmidt *et al.*, 1980). C5a summons neutrophils to the pulmonary vascular bed and the stimulated neutrophils release many products including oxygen free radicals, proteases, arachidonic acid metabolites and platelet-activating factor (acetyl glycerol ether phosphorylcholine, AGEPC) (Till *et al.*, 1982; Heffner *et al.*, 1983; Worthen *et al.*, 1983). Evidence suggests that proteases released from neutrophils can activate a number of inflammatory pathways such as activation of the Hageman Factor and its associated intrinsic coagulation pathway, complement sequence, kinin system and fibrinolysis (Reynolds, 1983). Many of these factors can directly injure the pulmonary endothelium and interstitium. This will be discussed later in the text. However, a number of these factors have neutrophil chemoattractant properties. Plasminogen activator, platelet activating factor, kallikrein and leukotriene B₄ may be important in amplifying the injury by attracting neutrophils to the lung. It has been demonstrated that when the pulmonary capillary endothelium is damaged by hyperoxia *in vitro*, neutrophils become increasingly adherent to the endothelium (Bowman *et al.*, 1983). Clearly, a vicious self-perpetuating cycle can be hypothesized from these data. A catastrophic clinical setting activates complement or the coagulation pathway, which in turn causes leucostasis and leucocyte entrapment in a fibrin matrix. The aggregated neutrophils release proteases, oxygen free radicals and other substances that injure the lung and attract more neutrophils, perpetuate complement activation, coagulation and synthesize more arachidonic acid metabolites to injure the lung.

Neutrophil injury

Neutrophils can damage the lung through a variety of mechanisms. Toxic metabolites derived from molecular oxygen, oxygen free radicals, have been implicated in lung injury for many years (Bowman *et al.*, 1983; McCord, 1983; Editorial, 1980; Sacks *et al.*, 1978; Weiss *et al.*, 1981). These include superoxide anions (O₂⁻), hydrogen peroxide (H₂O₂), singlet oxygen (¹O₂) and hydroxyl radical (·OH), and are generated by specific enzyme systems in neutrophils (Rinaldo and Rogers, 1982). Experimental evidence has suggested that activated oxygen metabolites also cause increased pulmonary vascular permeability and pulmonary vasoconstriction (Tate and Repine, 1982).

Several proteases are released by neutrophils. These proteases cleave Hageman Factor, complement, plasminogen and other plasma proteins (Till *et*

al., 1982). Thus, proteases have the potential deleterious effects of direct endothelial damage and amplification of injury through activation of other factors that injure the vascular bed. It is of interest to point out that the anti-elastase (alpha-1-protease inhibitor) has been shown to be inactive in patients with ARDS (Cochrane *et al.*, 1983a and b).

Arachidonic acid metabolites released by neutrophils are also of great importance in the pathogenesis of ARDS. Prostaglandins, thromboxanes and leukotrienes cause vasoconstriction, alter vascular permeability and are chemoattractants for neutrophils (Samuelson, 1983). Among the many products released by neutrophils is platelet activating factor, which causes platelet and neutrophil activation, smooth muscle constriction and increased vascular permeability in experimental models (Worthen *et al.*, 1983; Heffner *et al.*, 1983).

Coagulation product injury

According to clinical and experimental observations, pulmonary intravascular coagulation is associated with lung vascular injury (Saldeen, 1976; Carlson *et al.*, 1981). Disseminated intravascular coagulation was found in seven of 30 patients with ARDS in one series, and angiographically visualized pulmonary artery vascular occlusion was seen in 48% of patients with ARDS in another investigation (Bone, Francis and Pierce, 1976; Breene *et al.*, 1981). Platelet consumption with a reduced platelet life span and pulmonary sequestration of platelets is also significantly increased in patients with ARDS (Schneider, Zapol and Carvalho, 1980). Histologically, diffuse microvascular occlusion with fibrin and platelet thrombi and leucocyte aggregation are present (Hyers, 1981; Saldeen, 1976). The extrinsic and intrinsic coagulation cascades are activated by endotoxaemia, Hageman Factor, collagen exposed due to damaged endothelium and thromboplastin and proteases released from degranulating leucocytes (Wintrobe, 1981; Morrison and Ulevitch, 1978). Finally, it has been found that the fibrin degradation product, 'D antigen', was elevated in patients with ARDS, but not in a group of critically ill patients without ARDS (Haynes *et al.*, 1980).

These observations illuminated the possibility of coagulation products as either a cause or byproduct of ARDS, and led to a series of investigations to examine the role of microemboli, thrombin and fibrin degradation products (such as the 'D antigen') in the pathogenesis of ARDS. Selective depletion of blood components (platelets, neutrophils, fibrin, complement and inhibition of fibrinolysis) following micro-embolization in sheep and dog models demonstrated the pivotal role of several of the components (Malik *et al.*, 1983; Staub, Schultz and Albertine,

1982). Malik observed that neutrophils, fibrin, fibrin degradation products and complement are necessary for the development of ARDS following microembolization (Malik *et al.*, 1983). It was found that platelets are not necessary for the development of ARDS following microembolization. It seems probable that the vasoactive substances released from platelets such as serotonin and arachidonic acid metabolites, may aggravate the existing pulmonary hypertension. The possible deleterious interactions between complement and neutrophils in ARDS has been discussed. Coagulation products can also directly injure the endothelium. In experimental animals, the infusion of thrombin and 'D antigen', caused hypoxaemia, tachypnoea and increased pulmonary capillary permeability (Manwaring, Thorning and Curren, 1978; Malik and van der Zee, 1977).

Blockade of the reticuloendothelial (RES) system amplifies the effects of intravenous thrombin infusion on pulmonary vascular permeability and pulmonary hypertension. The RES plays a paramount role in the clearance of fibrin degradation products. Fibronectin is a 450,000 mol. wt. protein that is found on platelet membranes and throughout the reticuloendothelial system. Fibronectin acts as an opsonin to remove coagulation products and other circulating particles from the circulation. Fibronectin is depleted in clinical states that predispose patients to ARDS (Saba *et al.*, 1978). Thus, with less fibronectin as an opsonin of fibrin degradation products, these products have an extended time to injure the endothelium (Hyers, 1981).

Since the activation of intravascular coagulation causes complement activation both fibrin entrapment and complement mediated leucoaggregation may contribute to the development of ARDS following pulmonary intravascular coagulation (Malik, Johnson and Tahamont, 1982). It seems clear that the interaction of neutrophils, complement and coagulation products can amplify lung injury in ARDS.

Arachidonic acid metabolite injury

The increasing importance that prostaglandins, thromboxanes and leukotrienes seem to have in the pathogenesis of ARDS appears to parallel the increase in general knowledge that we gain about the products of arachidonic acid (AA) metabolism. Insults that injure the lung commonly stimulate the endogenous production of the biologically active metabolites of arachidonic acid.

Neutrophils, platelets and pulmonary endothelium are all potential manufacturers of arachidonic acid metabolites. A rapidly increasing body of evidence has suggested that these arachidonic acid products are important mediators of the bronchoconstriction, pulmonary vasoconstriction and increased pulmo-

nary vascular permeability that are pathognomonic of ARDS (Brigham *et al.*, 1983; Gee *et al.*, 1983; Garcia-Szabo *et al.*, 1983). A problem of primary importance in evaluating the role of arachidonate metabolites in ARDS is determining whether these compounds are a cause, a by-product or an epiphenomenon.

Pulmonary vascular resistance increases in patients with acute lung injury, and also in the majority of ARDS animal models (Brigham *et al.*, 1983). This increase in resistance alters Starling's forces in such a way as to encourage net transudation of fluid from the capillary to the interstitium and alveolar space. Several metabolites of arachidonic acid cause vasoconstriction, including prostaglandins E_2 , F_2 and H_2 (Demling, 1982; Brigham, 1982; Ogletree, 1982) arachidonic acid itself (Brigham *et al.*, 1983), and probably most importantly thromboxane A_2 (Harlan *et al.*, 1983; Kadowitz *et al.*, 1983). The rise in pulmonary vascular resistance has two distinct phases in unanaesthetized sheep. First, about an hour after endotoxin infusion, the pulmonary hypertension reaches a maximum, and, second, a moderate increase in pulmonary artery pressure occurs 3–5 hr after infusion. Cyclooxygenase and thromboxane synthetase inhibitors can inhibit the early pulmonary hypertension but not the second phase. This suggests that thromboxane is responsible for the first rise in pulmonary vascular resistance. Possibly the second rise in pulmonary vascular resistance is due to mechanical alterations in the lung secondary to injury and leak.

Increases in lung vascular permeability are also pathognomonic of ARDS. This is usually diagnosed clinically as diffuse bilateral pulmonary infiltrates and appears after an average of 27 hr after the initial insult (Fowler *et al.*, 1983). Leukotrienes C_4 , D_4 and E_4 all induce significant vascular permeability that seems to be caused by direct action on the vessel wall (Samuelson, 1983). Another potential mode of increasing vascular permeability by arachidonic acid metabolites, is the action of leukotriene B_4 to stimulate enzyme release and superoxide generation in human neutrophils (Palmlblad *et al.*, 1980). As discussed earlier, enzymes and oxygen free radicals from neutrophils increase pulmonary vascular permeability. Cyclooxygenase products do not seem to mediate this increase in pulmonary vascular permeability as demonstrated by (1) a lack of improvement with cyclooxygenase blockers; and (2) a lack of increased permeability after infusion of cyclooxygenase metabolites into experimental animals.

Decreased lung compliance is also seen in ARDS and is traditionally blamed on pulmonary oedema. Clinical and experimental observations have shown that pulmonary oedema is preceded by decreased

compliance. Thus, this decreased compliance might represent active constriction of airways. Thromboxane and leukotrienes have been implicated as aetiological factors in this bronchoconstriction (Brigham, 1982; Samuelson, 1983).

Finally, the metabolites of arachidonic acid have several positive effects, for example, prostaglandin E_1 and I_2 decrease lung injury after a variety of insults (Demling, 1982). In particular PGI_2 has vasodilator properties, anti-platelet aggregating properties and membrane stabilizing and anti-neutrophil aggregating properties (Demling, 1982).

Pathology

Although the causes of ARDS are extremely diverse, the pathological picture is remarkably similar. A useful classification of the microscopic pathological phases of ARDS has been proposed utilizing data primarily from lung biopsies (Pratt *et al.*, 1979; Lamy *et al.*, 1976). The onset of ARDS clearly must follow an insult to either the lung epithelia (aspiration of gastric contents, irritant gas inhalation, etc.) or damage to the pulmonary vascular endothelium (trauma, sepsis, disseminated intravascular coagulation, etc.). The lesions associated with this first phase include interstitial oedema, fibrin thrombi in small vessels, platelet and leucocyte aggregates, some hyaline membranes and often free alveolar oedema and extravasation of red blood cells into either the interstitium or alveolar space (Bachofen and Weibel, 1982; Hill *et al.*, 1976).

The type I alveolar epithelial cell is more sensitive to injury than the more resistant, cuboidal type II cell. Necrosis of the lung epithelia is present, primarily over the thinnest portion of the membrane where most gas exchange takes place. Surprisingly, there are no visible gaps in the capillary endothelium which could account for passage of protein-rich oedema fluid. In animal and human studies, the pulmonary oedema fluid in patients with ARDS often has the same concentration of proteins as the plasma (Urein, Snashall and Staub, 1976).

Despite recent advances in the understanding of the pathogenesis of ARDS the mortality is currently near 50% (Petty and Fowler, 1982). Among survivors the residual pulmonary sequelae tend to improve with time (Elliot, Morris and Cengiz, 1981; Rotman *et al.*, 1977). Residual problems that do persist after recovery include diffusion abnormalities and airflow obstruction (Lakshminarayan, Stanford and Petty, 1976; Rotman *et al.*, 1977).

Following lung damage in the first phase, the second phase is called the early progressive phase. The microscopic hallmark is hyaline membranes around the alveolar ducts. This amorphous eosinophilic layer is also seen concomitantly with marked

capillary congestion and interstitial oedema (Orell, 1971; Hill *et al.*, 1976). This phase is most prominent in specimens examined within 4–5 days after the initial insult (Hill *et al.*, 1976).

A large series of specimens has been examined from a multi-hospital collaborative study of extracorporeal membrane oxygenation as a potential therapy for ARDS. These data illustrate a late progressive phase of ARDS. Hyaline membranes, oedema and vascular congestion are decreased in extent and severity. The pathological hallmarks during this stage include interstitial fibrosis localized primarily in the alveolar ducts (Pratt *et al.*, 1979; Hill *et al.*, 1976). The pathological features seen in the late progressive stage of ARDS may be due in part to toxic oxygen radicals from neutrophils or from excessive oxygen administration. An increase in the number of cuboidal epithelial cells resembling type II pneumocytes is also a prominent feature of this phase (Bachofen and Weibel, 1982). Concomitant with the thickening of the interstitium, there is a decrease in the number of capillaries. The final phase is the late resolving stage where a gradual improvement in respiratory function occurs, presumably due to lysis of the interstitial fibrosis by alveolar macrophages (Hill *et al.*, 1976).

Upon examination of the gross pathological specimen it is evident that the tissue changes in ARDS at first are not homogeneous, and vary from one patient to the next (Pietra *et al.*, 1982). In the initial phase there are scattered areas of petechial haemorrhage, hyperaemia and 'congestive atelectasis' or alveolar collapse. During the early progressive phase there is widespread haemorrhagic and lobar consolidation. The lung becomes dark red, airless and indurated with a consistency like liver. Copious amounts of oedema fluid are often expressed from cut surfaces and fluid or blood may be present in pleural spaces. If resolution does not occur, the consolidation persists with a progressive fibrosis. At this point the lungs may become grey in colour with gross evidence of abscess, purulent bronchitis and thromboembolism often observed at autopsy.

In summary, the pathological features of ARDS include protein rich interstitial and alveolar oedema and small thrombi in the pulmonary vasculature (Urein and Staub, 1976; Urein *et al.*, 1976; Pietra *et al.*, 1982). Grossly the lung is heavy, oedematous and haemorrhagic. Later in the course of the syndrome hyaline membranes, marked capillary congestion and pulmonary oedema are seen. Subsequently, oedema and hyaline membranes decrease and interstitial fibrosis in response to injury ensues. Some patients go on to resolve a portion of the fibrosis with improvement of pulmonary function. In fact, approximately 85% of patients recovering from ARDS have very good pulmonary function (Elliot *et al.*, 1981).

Pathophysiology

A proposed pathophysiological scheme begins with the initial damage to the pulmonary capillary endothelium. This damage involves a change in the forces of the Starling equation to favour an exudation of protein rich fluid. It is clear that the integrity of the pulmonary capillary endothelium is lost. Extravasation of fluid ensues with initial accumulation in the lung interstitium. As the capacity of the alveolar walls is exceeded, the fluid begins to accumulate in the alveoli. The results of alveolar filling are increased surface forces and a collapse of alveoli in a diffuse pattern throughout the entire lung (Dantzker, 1982; Ralph and Robertson, 1981).

In the normal lung surfactant helps to balance alveolar surface forces and prevent alveolar collapse. However, surfactant abnormalities are present in patients with ARDS. Surfactant has been shown to be aggregated, oxidized and non-functional in ARDS patients. Surfactant is necessary for normal pulmonary function. With a loss of functioning surfactant the lung would be stiff (low compliance), have areas of atelectasis and alveoli filled with fluid (West, 1979). Indeed, these are the pathophysiological features of 'infant respiratory distress syndrome' and this disease is thought to be caused by a primary deficiency in surfactant. It seems apparent that the pathophysiological abnormalities associated with ARDS could partially be attributed to an inactivation of surfactant. These flooded and collapsed alveoli appear to cause many of the deleterious physiological alterations that are seen with ARDS.

Profound arterial hypoxaemia is a diagnostic criterion of ARDS. Ventilation-perfusion mismatch and right to left shunting are the mechanisms of this arterial hypoxaemia (Petty and Fowler, 1982; Teplitz, 1968; Case records, 1977; Wallace and Spence, 1983; Staub, Nagano and Pearce, 1967; Iliff, Greene and Hughes, 1972; Muir *et al.*, 1972). Utilizing an inert gas technique, it was demonstrated that shunt is the predominant mechanism of hypoxaemia (Dantzker *et al.*, 1979). The right-to-left shunt presumably results from blood flow through areas of alveolar oedema and atelectasis. Many patients also have low V/Q regions, although if a high $F_{I}O_2$ is used, these may not be clinically apparent (Watson, 1962). Ventilation-perfusion mismatch interferes with CO_2 elimination just as it causes an increased A-a O_2 difference. Regions of the lung with high V/Q result in an increased physiological dead space (Ralph and Robertson, 1981; Bachofen and Weibel, 1977). Unless minute ventilation increases there will be an increase in $PACO_2$.

ARDS is also characterized by reduced lung volumes and reduced compliance (Pontoppidan, Geffen and Lowenstein, 1972). The reduced lung volumes probably result from several mechanisms

including: (1) fluid-filled alveoli which occupy a smaller volume; (2) atelectasis; (3) compression of alveoli caused by interstitial oedema; and (4) increased surface tension due to decreased production and inactivation of surfactant (Fein *et al.*, 1982). The stiff, non-compliant lungs are manifest clinically by the high peak pressures required to deliver an adequate tidal volume. The decreased compliance in ARDS is due to a combination of active bronchoconstriction and interstitial and alveolar oedema (Snapper and Sheller, 1983; Sheller and Snapper, 1983). Unlike cardiogenic oedema, a significant body of evidence suggests that cyclooxygenase metabolites produce dramatic bronchoconstriction and subsequently reduced lung compliance in ARDS (Snapper and Sheller, 1983; Snapper *et al.*, 1981; Hinson *et al.*, 1982).

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