ACUTE RESPIRATORY DISTRESS SYNDROME;
INCIDENCE, PATHOPHYSIOLOGY
AND
SELECTED INTERVENTIONS

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ACUTE RESPIRATORY DISTRESS SYNDROME:
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Abstract

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May 2000

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Acute respiratory distress syndrome (ARDS) is a clinical response to a primary or secondary pulmonary injury or insult that is associated with severe hypoxemia. The incidence of ARDS has been reported between 1.5 and 75 cases per 100,000 population per year with mortality rates reaching 45-64 percent. ARDS is severe hypoxia with a PaO₂/FiO₂ < 200 torr from a non-cardiogenic pulmonary edema. ARDS is an end result of the Systemic Inflammatory Response Syndrome (SIRS), with a thick exudative fluid collecting in the pulmonary interstitium preventing the diffusion of oxygen across the alveolar-capillary membrane. Mechanical ventilation, supplemental oxygen and positive end expiratory pressure (PEEP) are the hallmark therapies of supportive care. The management goal for ARDS is to provide maximal oxygenation while decreasing iatrogenic complications of mechanical ventilation. Two interventions: the prone position and low tidal volume ventilation have been shown to improve oxygenation and mortality rates respectively for patients with ARDS.
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Acute Respiratory Distress Syndrome: Incidence, Pathophysiology, and Selected Interventions

Introduction

Acute respiratory distress syndrome is a clinical condition associated with severe hypoxemia that is refractory to oxygen therapy. It is characterized by the development of a thick exudative fluid in the alveolar-capillary interstitial spaces preventing the exchange of oxygen across the alveolar-capillary membranes. The inability to oxygenate and ventilate creates systemic and cellular hypoxia, acidosis, and death (Wiedemann & Tai, 1997).

First described in 1967, Ashbaugh, Bigelow, Petty & Levine identified a form of respiratory distress that was associated with non-cardiogenic pulmonary edema and named it adult respiratory distress syndrome. This syndrome lacked specific diagnostic criteria until the American-European Consensus Conference (AECC) in 1992. During this conference specialists met and developed the diagnostic criteria and changed the name to Acute Respiratory Distress Syndrome (ARDS). The AECC provided the medical community with two important definitions. First they defined specific requirements for the diagnosis of ARDS and second they defined criteria for Acute Lung Injury (ALI), the precursor to ARDS (See Table 1).

Between 1967 and 1992, clinicians diagnosed patients with ARDS using a variety of criteria and definitions. Diagnostic inconsistencies have challenged research interpretation by using different levels of hypoxemia or clinical presentations to diagnose ARDS and enroll subjects into research studies. The
ability to define and diagnose ALI and ARDS accurately and consistently is paramount in understanding the incidence of ARDS. Since 1967, the estimated incidence of ARDS has ranged from a high of 71 cases per 100,000 population per year (National Institute of Health, 1972) to a low of 1.5 cases per 100,000 population per year (Villar & Slutsky, 1989). These studies used different definitions and severity of illness criteria to define ARDS. Using the AECC definition, Luhr et al. (1999) estimated that the combined incidence of ALI and ARDS is 31.4 cases per 100,000 population per year.

Understanding the incidence of ARDS is important because of the costly medical care and high mortality rate associated with the disease. The severe hypoxemia associated with the disease, requires mechanical ventilation and prolonged hospital admissions. Several authors have reported hospital admissions stays between 3-50 days (Dunham, Damiano, Wiles, & Cushing, 1995; Thelan, Urden, Lough, & Stacy, 1998; Hudson & Steinberg, 1999). The shorter number of days is related to a higher early mortality rate, whereas, survivors require several weeks of mechanical ventilation (Thelan et al., 1998; Hudson & Steinberg, 1999). Understanding the impact on mortality and medical expense will allow researchers to quantify the impact on society when requesting research funds for prevention and treatment.

Using the AECC definition, the mortality of ARDS has been reported to be 45% to 64% with a significant increase for persons over 55 years of age (Suchyta et al., 1997). Mortality from ARDS is estimated to be between 40,000 – 70,000 cases per year. To provide perspective Matthay (1999) compared the ARDS
mortality to the better-known and recognized disease breast cancer, which has a mortality of 45,000 cases per year.

Trauma-related causes of ARDS are of particular interest for two reasons. First, mortality increases 30-45% with the combination of organ failure (ARDS) and traumatic injuries compared to isolated traumatic injuries (Dunham et al., 1995; Hudson, Milberg, Anardi, & Maunder, 1995). Second, traumatic injuries have a clear and identifiable time of injury, hence marking the initial activation of the normal inflammatory response and progression to the pathologic Systemic inflammatory Response Syndrome (SIRS). Understanding the early sequence of events may allow clinicians and researchers to determine positive predictive markers to identify patients at high risk for the development of ARDS.

ARDS is a secondary response to injury and a primary effect of the SIRS, therefore much of the care is supportive and reactive to disease severity. For 30 years the standard therapy for ARDS has been aimed at maintaining an adequate level of oxygenation and supporting the patient through the physiologic derangement caused by the inflammatory response. Supplemental oxygen and incremental positive end expiratory pressure (PEEP) to improve oxygenation and ventilation have remained the essential treatment for ARDS.

Recent investigations using surfactant (Hartog, Gommers, & Lachmann, 1995), ketoconazole (Devries, Semchuk, & Betcher, 1998; ARDS Network, 2000), antioxidants, (Laurent et al., 1996), and nitric oxide (Ludin et al., 1999) have failed to show significant patient improvement in patients with ARDS. Trials using positioning (Fridrich et al., 1997) and low tidal volume ventilation therapy
(The ARDS Network, 2000) have been shown to improve oxygenation and decrease mortality rates, respectively.

ARDS and ALI share many similarities with the only difference being the degree of hypoxemia. Being a precursor, patients develop ALI prior to progressing to ARDS. To date, researchers have been unable to accurately predict which high-risk patients with ALI will develop ARDS; therefore many clinical trials have targeted those with severe hypoxemia and ARDS. The identification of accurate biophysical markers that are easily obtainable and affordable will enable researchers and clinicians to focus investigations towards prevention strategies and interventions to reduce the progression and severity of ALI and ARDS.

The purpose of this paper is to examine the epidemiology, describe the known pathophysiology of ARDS, and evaluate the research evidence of two experimental interventions suggesting improved outcomes: the prone position (Fridrich et al., 1997) and low tidal volume ventilation (ARDS Network, 2000). An understanding of these interventions may improve the delivery of patient care, decrease mortality, and decrease medical expenses incurred with prolonged intensive care requirements.

**Epidemiology**

**Incidence.**
The incidence of ARDS has been questioned for some time, with the exact numbers being uncertain. In 1972, the NIH reported the incidence of ARDS to be
71 cases per 100,000 persons hence affecting about 150,000 persons in the United States in 1972. These numbers were thought to be excessive prompting researchers to explore the incidence of ARDS. In 1985, Villar and Slutsky examined the incidence of ARDS in the Canary Islands, estimating the incidence to be between 1.5 and 3.9 cases per 100,000 population per year. Lewandowski et al. (1993) used the Lung Injury Score (see table 2) reporting the incidence to be 3.0 persons per 100,000 population per year in Germany. Thomsen and Morris (1995) studied the incidence of ARDS in the state of Utah. Using discharge diagnosis and zip codes, researchers calculated the incidence of ARDS in the state of Utah to be between 4.8 and 8.3 persons per 100,000 population per year. Evans, Wachter, Wiener-Kronish & Luce (1989) published an abstract reporting the incidence of ARDS in San Francisco to be as high as 25 persons per 100,000 population per year. This study examined persons over the age of one year who developed ARDS but was limited by the failure to use consistent diagnostic criteria in determining the diagnosis of ARDS and the high rate of pneumocystis carinii pneumonia related ARDS.

In contrast to previous incidence studies, Luhr et al. (1999) conducted a prospective study of intensive care units in the countries of Sweden, Denmark, and Iceland; the researchers identified 508 persons over the age of 15 who met the AECC definition of ALI and ARDS. The investigators estimated the incidence of ALI and ARDS to be 17.9 per 100,000 population and 13.5 per 100,000 population respectively. Further, the investigators determined that using the diagnostic criteria of \( \text{PaO}_2/\text{FiO}_2 \) ratio < 110, decreased the incidence to 3.7 cases
per 100,000 per year. These research discrepancies demonstrate the inadequacies of the available data to reliably determine the prevalence of ARDS in the United States. Researchers and clinicians need current and accurate data in order to understand the physical, emotional and financial impact on society. The lack of consistent data supports the need for prospective studies that use standardized diagnostic criteria (See Table 3).

Risk factors.

Several factors have been associated with an increased risk of developing ARDS. Some of these clinical situations include: sepsis syndrome, aspiration of gastric contents, pulmonary contusions, multiple blood transfusions, near drowning, and pancreatitis (Garber et al. 1996; Bass, Miller, Campbell, & Russell, 1997). Burns, multiple long bone fractures, and coronary artery bypass graft surgery are also associated with an increased risk of developing ARDS (Connelly & Repine, 1997). Hudson et al., (1995) conducted a prospective study between 1983 and 1985 to examine the risk factors associated with development of ARDS. The investigators identified 695 patients who met the inclusion criteria of at least one of the seven high-risk groups including: sepsis syndrome, multiple transfusions, near drowning, pulmonary contusion, aspiration, multiple fractures, and drug overdose. The data identified 179 of 695 patients who developed ARDS during this three-year study. There were 48 additional cases of ARDS that were not identified as high-risk giving an overall sensitivity of 79% to the seven high-risk groups. Within the 179 prospectively identified cases of ARDS, sepsis
syndrome accounted for 76 cases (42.6%) followed by 69 traumatic related injuries (38.5%). The incidence of ARDS increased with a combination of two or more of the following: pulmonary contusions, massive transfusions, and multiple fractures (Hudson et al., 1995). These results identified an increased risk of developing ARDS for each of the seven high-risk groups; however, differences between the high-risk ARDS group and the high-risk non-ARDS group were not significant with respect to age, gender, severity of illness, acidosis, or serum bicarbonate. Limitations of this study included a unique definition of ARDS that is not consistent with the AECC definition and the study facility being a Level-I Trauma and ARDS referral center. Although these seven high-risk groups are 79% sensitive, they are only 26% specific. Additional studies identifying high-risk patients are needed to guide researchers and clinicians in early identification, prevention and management of ARDS.

**Physiology, Pathophysiology and Clinical Manifestations**

Inflammation and activation of the immune system is a normal physiologic response to injury or infection. Complement, cytokines, and nitric oxide are part of the initial inflammatory response to infection or injury within the body. These chemical mediators trigger inflammation while stimulating the migration of macrophages and other substances that are essential to fight infection and repair injured cells. Specific proteins regulate excessive cytokine production limiting the inflammatory response (Davies & Hagen, 1997). The immune and inflammatory response is an extensive and complex process that exceeds the scope of this
paper. This section will examine the pertinent physiology as it applies to pulmonary function and ARDS.

**Pertinent Physiology.**

Alveolar gas exchange occurs by simple diffusion of gasses from a high concentration to a lower concentration across the alveolar-capillary membrane. The rate of diffusion is directly related to the surface area, the diffusion coefficient of the gas, and the difference in the partial pressure. The rate of diffusion is inversely proportional to the thickness of the membrane over which the gases travel across (Costanzo, 1998). Pulmonary ventilation is the function of respiratory muscles, which actively contract to bring oxygen and other gases to the alveoli, while alveolar respiration is the process of gas exchange (Berne & Levy, 1990; Costanzo, 1998). Alveoli are pouch-like invaginations in the terminal bronchi. These pouches are thin and have a large surface area to exchange gas with the pulmonary circulation (Costanzo, 1998). Pulmonary capillary blood flow is initially high in carbon dioxide levels. Once the blood vessel comes into contact with the alveolus, carbon dioxide diffuses across the capillary membrane then across the alveolar membrane and is removed from the body during exhalation. There is a higher concentration of oxygen in the alveoli compared to the pulmonary capillary, which diffuses across the alveolar membrane, then across the capillary membrane where it is bound to hemoglobin and transported to the cells for cellular respiration (Berne & Levy, 1990). A diffusion limited ventilation-perfusion mismatch occurs when oxygen is unable to diffuse across the alveolar
capillary membrane, such as when interstitial exudate develops with ARDS (Costanzo, 1998).

The inflammatory response is a complex interaction of sub cellular proteins and enzymes in response to injury or infection. An initial process in the inflammatory cascade is the activation of complement. Complement is an enzymatic cascade of proteins that respond either to an antigen-antibody complex (Classical pathway) or a microbial or abnormal cell surface (alternative pathway). Each protein was named in the order of discovery and was given a sequential number (Complement 1 [C1], Complement 2 [C2] etc.). In vivo, complement is continually circulating and interacting with cells. The trigger point in both pathways is the conversion of C3 into C3a and C3b, with C3a causing activation and C3b causing amplification of the complement cascade. Normal cells have a binding protein to prevent amplification. In contrast, injured cells and bacteria lack the binding protein to inhibit an exponential increase of complement activity. Normally C3a has a short bioavailability and limited systemic reactions, however when C3b amplification occurs, increased production of C3a triggers the release of large numbers of inflammatory chemicals called cytokines. C3b binds with factor B and factor D to cleave C5 into C5a and C5b. C5a is a small molecule that attracts neutrophils and stimulates additional cytokine release resulting in neutrophil aggregation to endothelial cells (Manifold, 1995; Clough & Roth, 1998). C5b activates the membrane attack complex, which initiates a series of protein conformations injuring the cell membrane, eventually resulting in cellular death (Clough & Roth, 1998). Cytokines are small proteins that have a
variety of functions including pro-inflammatory, anti-inflammatory, cellular stimulation, and cellular identification. In concert with complement, cytokines have an important role in a physiologic inflammatory response. Exaggerated production of complement and cytokines may result in detrimental effects including injury to the pneumocytes.

Type II pneumocytes are cells located in the alveoli and have important physiologic and pathologic implications for ALI and ARDS. Type II pneumocytes are cellular precursors for type I pneumocytes, which cover 95% of the alveolar surface and permit the diffusion exchange of $O_2$ and $CO_2$ across the alveolar-capillary membrane (Lwebuga-Mukasa, 1998; Costanzo, 1998). Other functions of type II cells are the production of surfactant and expression of inducible nitric oxide synthase (iNOS). Surfactant is phospholipid that reduces the surface tension of the alveoli, preventing atelectasis (Lwebuga-Mukasa, 1998; Costanzo, 1998; Curzen, Jourdan, & Mitchell, 1996). Nitric oxide is formed when iNOS combines with l-arginine (an amino acid) producing dilatation of the pulmonary vascular smooth muscle, increasing pulmonary perfusion of inflammatory, and bacteriocidal chemicals needed to respond to infection (Lwebuga-Mukasa, 1998; Costanzo, 1998; Davies & Hagen, 1997). Excessive production of NO may cause damage to normal cells and creation of cytotoxic substances such as hydroxyl radicals (Lwebuga-Mukasa, 1998; Davies & Hagen, 1997; Curzen, Jourdan, & Mitchell, 1996). Hydroxyl radicals produce cellular damage by degrading essential cellular components and amplifying the inflammatory process. Further hydroxyl radicals stimulate the upregulation of several pro-
inflammatory cytokines and cellular adhesion molecules (Davies & Hagen, 1997). The additive effect of NO on the inflammatory process is beneficial, but can contribute to the progressive pathologic SIRS.

The inflammatory response system is an effective and essential component to repair and defend the body (Clough & Roth, 1998). Activation and amplification occur as a physiologic response, however when the homeostasis is not maintained, a severe inflammatory response called the Systemic Inflammatory Response Syndrome (SIRS) may occur (Davies & Hagen, 1997). The uncontrolled activation of the SIRS can affect one or several organ systems in the body including the lungs, heart, liver and kidneys (Moore et al., 1996). When this pathologic inflammatory cascade occurs in the lungs, ALI and ARDS may develop (Davies & Hagen, 1997).

**Pathophysiology and clinical manifestations.**

With respect to traumatic injury and the development of acute lung injury, the inflammatory response is activated by two main mechanisms. The first mechanism is a direct injury to the alveolar-capillary beds with blunt trauma, penetrating trauma, or aspiration. The second mechanism can occur through non-pulmonary injury such as systemic hypoperfusion hypoxia or sepsis.

Direct injury to the alveolar-capillary membranes activates a normal systemic inflammatory response and can progress to severe hypoxemia and ARDS from normal cellular function. Non-pulmonary injury from prolonged episodes of hypovolemia and hypoperfusion results in a cellular hypoxia and
oxygen debt. During the initial stages of shock, a decreased mean arterial pressure triggers the activation of the sympathetic nervous system with release of catecholamines (Neff, 1993). Catecholamines cause arterial and venous constriction maintaining perfusion of essential organs such as the brain, heart and liver. Arterial constriction diverts blood flow from non-essential tissues including the extremities and gastrointestinal tract (Neff, 1993). The hypoperfusion results in hypoxia changing the cellular function from aerobic metabolism to anaerobic metabolism producing inadequate energy stores (AMP and ADP instead of ATP) as well as deoxygenated metabolites (Seigle, 1997). With restoration of intravascular volume and tissue perfusion, reperfusion of these metabolites creates superoxide and hydrogen peroxide radicals that stimulate an inflammatory response. Activation of the inflammatory response without a specific tissue or organ injury results in sequestration and margination of neutrophils to pulmonary endothelial cells (Quinlan et al. 1997).

After an initial injury or triggering event, neutrophils are released into the circulation to marginate along endothelial cells, waiting for activation. As complement is released, C3a stimulates neutrophils to express intracellular agglutination molecule (I-CAM). I-CAM tightly binds the neutrophils to the endothelial walls (Hecke et al. 1997). The exudative phase of ARDS develops as neutrophils migrate between capillary endothelial cells (diapedesis) arriving in the alveoli-capillary interstitium. Movement of neutrophils across the endothelial membrane causes structural damage to the pulmonary endothelium (Palister, Gosling, Alpar, & Bradley, 1997) allowing larger molecular proteins such as
albumin to exit the vascular space. These structural changes create additional injury to the vascular beds, increasing the interstitial oncotic pressure, and continued stimulation of the inflammatory response (Moss et al. 1996). The mixture of high protein fluid and neutrophils creates a collection of thick exudative fluid increasing the diffusion distance of the alveolar-capillary membranes, thus limiting diffusion of oxygen (Prendergast & Ruoss, 1995). As this collection of fluid increases, a pathologic shunt develops, resulting in capillary hypoxemia (Costanzo, 1998). This shunt is the pathologic factor associated with the severe hypoxemia of ARDS.

Clinical findings of early ARDS include tachycardia, tachypnea and a progressive decrease in the partial pressure of arterial oxygen (PaO₂). The chest radiograph demonstrates diffuse hazy, patchy infiltrates throughout all lung fields and patients usually require mechanical ventilation by the end of the exudative phase (Tremblay & Gursahaney, 1998).

A second phase, the proliferative stage, occurs over the next several days. The inflammatory cascade increases in response to the abnormal collection of fluid in the pulmonary interstitium thus increasing hypoxemia. The increase in pulmonary exudate causes a worsening hypoxemia requiring a higher fraction of inspired oxygen (FiO₂) and the addition of PEEP in order to maintain arterial oxygenation (Tremblay & Gursahaney, 1998). Neutrophils continue to diapedes between the endothelium cells activating additional complement and cytokines, thus increasing edema of the pulmonary interstitium. Continued stimulation of the inflammatory response is known to activate thrombin and
platelet aggregation and may lead to disseminated intravascular coagulation (Gando, Kameue, Nanzaki, Hayakawa, & Nakanishi, 1997).

The third phase of ARDS is the migration of thrombin and fibrin into the pulmonary interstitial spaces binding with neutrophil elastase to create fibrin and collagen lattice fibrosis. Thrombin stimulates the inflammatory process, increasing the endothelium cellular gaps caused by neutrophil diapedesis (Donnelly et al., 1995; Gando et al. 1997). The collection of pro-inflammatory chemicals, neutrophils and macrophages in the pulmonary interstitial spaces damages the type I pneumocytes. To replace the damaged type I cells, type II pneumocytes are converted to Type I cells resulting in decreased surfactant production. A lack of surfactant increases the alveolar surface tension and decreases pulmonary compliance (Lwebuga-Mukasa, 1998).

Clinical Management

Since ARDS was first described in 1967, primary management has been supportive care. The interstitial exudate decreases the ability to exchange oxygen across the alveolar-capillary membrane and decreases pulmonary compliance resulting in atelectasis and poor oxygenation. Without mechanical ventilation, supplemental oxygen and PEEP, these patients would continue to become hypoxic and expire. The supportive goal is to provide optimal oxygenation keeping the FiO₂ as low as possible while using tidal volumes of 10-15cc/kg and PEEP to facilitate oxygen exchange. These essential therapies are associated with significant risks including iatrogenic pneumothorax (Tremblay &
Gursahaney, 1998; Lwebuga-Mukasa, 1998; Finfer & Rocker, 1996), and pulmonary stretch injuries (Slutsky, 1999) causing additive complications to an already compromised patient. Maintaining oxygenation, fluid and electrolyte status, and appropriate antibiotic therapy indicated by the clinical course are standard treatment plans (Weidmann & Tai, 1997; Schuller, 1998; Tremblay & Gursahaney, 1998).

With an advanced understanding of ARDS, investigators have explored a variety of treatment options including the use of anti-inflammatory pharmaceuticals, surfactant replacement, nitric oxide, prone position, and low tidal volume ventilation. Pharmaceuticals such as ketoconazole, prostaglandin-E, and antioxidants have been studied in multi-center double blind randomized controlled trials and have failed to demonstrate a benefit in the treatment of ARDS (Tremblay & Gursahaney, 1998).

Surfactant therapy was believed to be beneficial by replacing the degraded surfactant products that are disrupted by pulmonary inflammation and fibrinolysis; however, the use of surfactant replacement failed to show benefit in the management of ARDS in adults (Hartog, Gommers, & Lachmann, 1995).

Inhaled nitric oxide (NO) causes selective pulmonary vasodilatation without systemic effects. It was believed that NO would increase pulmonary blood flow and oxygenation. A European multi-center randomized controlled study evaluated the progression of ALI to ARDS and the use of NO (n=268). The results demonstrated a significant difference between ALI progressing to ARDS and ALI that did not progress in patients receiving NO (10.3% v. 2.2%, p<0.05);
however the overall mortality between the two groups was not significantly different (Lundin et al., 1999). Further studies are continuing to determine if a role exists for the use of NO in the management of ARDS.

Prone Position.

Prone position therapy is a method that may improve arterial oxygenation in patients with ALI and ARDS. The interstitial exudate of ARDS is a thick tenacious collection of neutrophils and fibroblasts that settles in dependent areas of the lungs impairing oxygen exchange (Gattinoni, Pelosi, Vitale, et al. 1991). It is believed that the prone position improves both ventilation and oxygenation by changing the pulmonary blood flow and ventilation distribution to newly dependent areas of the lungs (Costanzo, 1988; Berne & Levy, 1990). Recently the use of the prone position has resurfaced as a method to improve oxygenation in patients with ALI/ARDS. The use of the prone position has been shown to improve PaO₂ and PaO₂/FiO₂ ratio in several studies (Fridrich et al., 1996; Vollman and Bander, 1996; Chatte et al., 1997; Pelosi, Tubiolo et al., 1998; & Jolliet, Bulpa, & Chevrolet, 1998).

Fridrich et al. (1996) examined 20 patients with AECC defined ARDS and serious traumatic injuries with an Injury Severity Score greater than 16. Using a quasi-experimental design subjects were placed in a prone position for 20 hours followed by four-hour supine periods. Data were collected one hour before and one hour after each turn cycle. These findings demonstrate a change in the mean PaO₂/FiO₂ ratio from 126.4, 204.1, 247.2, and 162.4 at 1 hour prior to
prone, one hour after being turned prone, 19 hours after being turned prone and, one hour after being turn supine, respectively, during the first 24 hours. Comparable findings were observed during the sequential 92 hours of the study. Although 100% of the patients responded to the prone position with decreased shunt, two subjects (10% of total study group) experienced death (Fridrich et al. 1996).

Chatte et al. (1997) studied 32 patients in a quasi-experimental design with severe non-cardiogenic respiratory failure with combinations of ARDS, sepsis and, pneumonia. All of the subjects had a PaO2/FiO2 ratio of <150 with FiO2 > .50, no evidence of left ventricular failure, and required mechanical ventilation. The subjects were given a one hour trial of the prone position and deemed non-responders if the saturation of oxygen (SaO2) decreased by 5% or if the PaO2/FiO2 ratio did not increase by 20 mm Hg. Seven patients (22%) were non-responders while the remaining 25 patients (78%) demonstrated a mean change in PaO2/FiO2 from 103 to 158, 159, 128 at baseline, 1 hour prone, 4 hours prone, and 1 hour supine respectively (p<0.001). The overall mortality rate was 56%. A majority of the deaths (14/18) were associated with multiple organ failure and occurred an average of 18 days after initiation of the prone position therapy (Chatte et al., 1997).

Jolliet, Bupa, and Chevrolet (1998) examined 19 patients with severe ARDS (PaO2/FiO2 < 150, for >24 hours, despite FiO2 > 0.60) to see if the prone position would improve oxygenation. The study evaluated patients for levels of responsiveness at 2 and 4 hours in the prone position. Those who responded
were placed in the prone position for 12 hours, while those who were non-responsive were reassessed each day. Fifty-seven percent (11/19) of the sample, the responders, demonstrated a change in the mean PaO2/FiO2 ratio from 68 to 93, 88, 105 at baseline, 30 minutes, 120 minutes, and 12 hours, respectively. These data indicate the most dramatic change occurred within the first 30 minutes, however a continued improvement was seen after 12 hours. The overall mortality rate was 79% suggesting that advanced ARDS has a high mortality rate (Jolliet, Bupa, & Chevrolet, 1998).

Pelosi, Tubiolo, et al. (1998) investigated gas exchange, physiologic dead space and, end expiratory lung volume (EELV) in 16 patients with AECC criteria for ALI/ARDS using a quasi-experimental design. Results demonstrated a mean change of PaO2 from 103 mm/Hg to 119 mm/Hg, 129 mm/Hg, 123 mm/Hg and 117 mm/Hg at baseline, 30 minutes prone, 120 minutes prone, 30 minutes supine, and 120 minutes supine, respectively. These data demonstrate a net increase of the PaO2 of 14 mm/Hg four hours after returning a patient to a supine position. This study failed to demonstrate a significant change in physiologic dead space or EELV and warrants future investigations to evaluate alveolar recruitment as a source of increased oxygenation (Pelosi, Tubiolo, et al., 1998).

Placing the patient in the prone position is a labor-intensive procedure that requires either three people using a portable support frame (Vollman Prone Positioner; Hill-Rom, Bates Ind.) or five people using pillows. This is the minimum number of people recommended to turn the patient safely and manage the endotrachial tube and intravenous access lines (Vollman and Bander, 1996). The
most common adverse effect of placing a patient in the prone position is facial edema, followed by pressure ulcers on the chin and forehead, and contractures of the arms (Fridrich et al., 1996; Chatte et al., 1997; Pelosi et al., 1998; Jolliet et al., 1998).

Despite the improvement in oxygenation and absence of serious reported complications associated with the prone position, there are several unanswered questions regarding the role of prone position therapy in the management of ARDS. Further investigations are warranted to gain a better understanding of mechanisms by which the prone position increases oxygenation. In addition, understanding if the prone position decreases mortality, duration of mechanical ventilation, and length of stay in intensive care units needs to be explored in future prospective randomized controlled studies to determine efficacy. Prospective randomized controlled trials (PRCT) should be conducted to establish a time period in which prone position therapy optimizes oxygenation while minimizing the adverse effects.

**Low Tidal Volume Ventilation.**

The severity of hypoxemia that patients with ARDS experience requires mechanical ventilation (MV) to enhance oxygen delivery and ventilation. The use of MV can be associated with untoward consequences including lung volutrauma, barotrauma, and biotrauma (Slutsky, 1999). Volutrauma is defined as diffuse alveolar damage that occurs as a result of over inflation or stretch injury to the alveoli in response to moderate to high tidal volumes (Slutsky, 1999;
Barotrauma occurs in the presence of high airway pressures resulting in alveolar damage. Barotrauma differs from volutrauma in that barotrauma occurs with high pulmonary pressures, whereas volutrauma can occur with large volumes and low pressures (Weidmann & Tai, 1997; Slutsky, 1999; Gannon, Wiswell & Spitzer, 1998; Finfer & Rocker, 1996). Biotrauma is a pattern of injury occurring with MV resulting in alveolar inflammation with sequesterization of neutrophils and other cellular mediators (Slutsky, 1999). Mechanical ventilation is required to support patients with ARDS, but has a propensity to cause additional lung injury (Slutsky, 1999). In an effort to reduce the iatrogenic complications of MV, several studies have investigated the use of lower tidal volumes in the management of ARDS (Amato et al., 1998; Stewart et al., 1998; Brochard, et al. 1998; & Brower et al., 1999; The ARDS Network, 2000).

Mechanical ventilation (MV) is a cornerstone in the enhanced delivery of oxygen to the alveolar capillary beds and removal of carbon dioxide. Since 1970 there have been several MV treatment protocols for ARDS. It was initially thought the use of large tidal volumes and high PEEP levels would recruit more alveolar beds and improve oxygenation (Pelosi, Cardringer, et al., 1999; DeGuia, 1996). PEEP is an airway pressure applied with MV to keep the alveolar sacs expanded during exhalation, thus decreasing the work of breathing and improving oxygen and carbon dioxide exchange across the alveolar-capillary membrane (Gattinoni, Pelosi, Crotti, & Valenza, 1995). The benefit of high tidal volumes was questioned when several animal studies (Dreyfuss, Basset, et al., 1985; Kolobow
et al., 1987; Dreyfuss, Soler et al., 1988) demonstrated that high tidal volumes resulted in high pulmonary pressures causing pulmonary endothelium injury. Tusno, Prato, & Kolobow (1990) suggested that high-pressure ventilation caused acute lung injury and exacerbated the clinical presentation of ALI and ARDS.

Recent studies (Amato et al., 1998; Stewart et al., 1998; Brochard, et al. 1998; & Brower et al., 1999) used PRCTs to compare standard ventilation (tidal volume of 10-12 ml/kg) to low tidal volume ventilation (tidal volume of 6-8 ml/kg). These studies controlled peak inspiratory pressures (PIP) and plateau pressures while adjusting PEEP and FiO2 to provide optimal oxygenation and alveolar recruitment. All four of these studies had small sample sizes (53, 120, 116, & 52 respectively) and failed to demonstrate improved overall mortality rates with low tidal volume ventilation strategies.

The study by Amato et al. (1998) demonstrated improved mortality rates for patients receiving a lower tidal volume compared to standard tidal volumes (11/29 v 17/24 respectively; p<0.001) at 28 days. Results indicated that successful weaning from MV was greater in the low tidal volume group (66% v 29%; p=0.005) as was the decrease in the incidence of barotrauma (7% v 42%; p= 0.02). Despite the initial improvements, the mortality rate at hospital discharge was not significantly different (45% v 71%; p=0.37) (Amato et al., 1998).

Stewart et al. (1998) examined subjects who were at risk for developing ARDS. His results indicated no significant difference in mortality, incidence of barotrauma, or multiple organ failure between the low tidal volume group and the control group. Brochard et al. (1998) and Brower et al. (1999) both examined
patients with AECC criteria for ARDS and used mean tidal volumes of 7cc/kg and 10cc/kg. Results showed no difference in mortality rates, duration of MV, incidence of pneumothorax, or multiple organ failure.

The ARDS Network (2000) completed a large multi-center PCRT to evaluate the effects of low tidal volume ventilation (6cc/kg) compared to standard tidal volume ventilation (12 cc/kg). The primary end point was mortality with secondary end points including duration of MV and occurrence of multiple organ failure. The study enrolled 861 patients from ten centers, all of whom were intubated, mechanically ventilated and, fulfilled AECC criteria for ALI and ARDS. Subjects were randomized to either receive a low tidal volume (LTV) of 6 cc/kg or a traditional tidal volume (TTV) of 12 cc/kg. After adjustments in tidal volume, optimal oxygenation was achieved by adjusting the FiO₂ and PEEP. The study was stopped early because of a significant decrease in mortality rates (LTV: 31% v TTV: 39.8%; p=0.007). There were reported improvements in the PaO₂/FiO₂ ratio and a decrease in multiple organ failure for the LTV group compared to TTV group. The large sample size and the study design suggest improvement with the use of smaller tidal volumes in the treatment of ARDS, however this study is limited by the use of a large exclusion criteria list. These criteria included: if > than 36 hours had elapsed since meeting the diagnostic criteria, under the age of 18 years old, pregnant, increased intracranial pressure, neuromuscular disease that could impair spontaneous breathing, sickle cell disease, severe chronic respiratory disease, weighed more than 1 kg/cm of height, > 30% burns to body surface area, presence of other conditions associated with 50% mortality rate at
six months, received a bone marrow or lung transplant, chronic liver disease, or the attending physician was unwilling to use full life support (The ARDS Network, 2000). These data indicate a significant improvement in those patients who met the inclusion criteria, however these results may not be generalizable to all ARDS populations. Additional studies are needed to confirm and enhance the application of these data.

Conclusions

Acute Respiratory Distress Syndrome has been a clinical challenge in critical care and pulmonary care for over 30 years. The end result of a pathologic systemic inflammatory response, ARDS is responsible for severe hypoxemia and resultant hypoxia, prolonged intensive care, and a high mortality rate. In combination with multiple system disease, or injuries, ARDS is often devastating. Little advancement has been made in the management of ARDS other than supportive care, and researchers are still trying to identify predictive markers and effective treatments.

Between 1967 and 1992, ARDS was a term that described severe hypoxemia that was refractory to supplemental oxygen and characterized by a large pulmonary shunt. There were no specific defining characteristics to guide clinicians in diagnosing ARDS. The absence of specific criteria has resulted in 25 years of research that used different degrees of hypoxemia and severity making comparison difficult. The incidence of ARDS has been estimated between 3 and 71 cases per 100,000 population per year. In reality these estimates examined
different degrees of ALI, some having a wide range of inclusion criteria and others with limited criteria. The work of Luhr et al. (1999) illustrated that earlier studies failed to include actual cases of ARDS because of inconsistent criteria. There was a 365% increase in the incidence of ARDS when using AECC criteria compared to criteria used in previous studies. When comparing the incidence of ALI and ARDS to previous study criteria, there was an 849% increase (Luhr, 1999). These results represent one study in one geographic area. The true incidence of ARDS and ALI continues to be unknown. Additional controlled studies using a single set of criteria must be conducted to achieve accuracy in incident reporting.

The American-European Consensus Conference provided clinicians the single most important advancement in the study of ARDS, a standardized diagnostic definition. Armed with criteria to make an accurate diagnosis and measure the severity of ALI and ARDS, rigorous research can occur knowing that the results can be compared with other studies to advance theory leading to evidence-based practice. Past studies of anti-inflammatory medications and surfactant replacement have not demonstrated improved mortality rates. Even though these interventions have not proven effective in improving mortality rates, the actual effect will not be known until the studies are conducted using the AECC guidelines.

Supplemental oxygen, mechanical ventilation, and PEEP have been the hallmark of supportive ventilatory care for persons who develop ARDS. Recent studies of the prone position (Amato et al. 1998) and low tidal volume ventilation
(The ARDS Network, 2000) have suggested improvements in oxygenation and mortality rates respectively. The use of the prone position is a labor intensive intervention demonstrating improved oxygenation in patients with ARDS. Before the prone position can be recommended as a beneficial therapy for ARDS, additional studies need to be performed to determine the overall mortality rate while establishing procedural protocols to decrease the risk of inadvertent removal of intravenous access and artificial airways. The researchers (Fridrich et al., 1996; Vollman and Bander, 1996; Chatte et al., 1997; Pelosi, Tubiolo et al., 1998; & Jolliet, Bulpa, & Chevrolet, 1998) have reported varying periods of time patients remained in the prone position. Understanding a distinct period of time that provides optimal oxygenation without the development of adverse effects will improve the application and safety of this intervention. Future PRCTs should be conducted before this intervention is utilized routinely in patient care.

The ARDS Network has presented evidence to support the use of low tidal volume ventilation reporting a 22% decrease in mortality (ARDS Network, 2000). This was a multi-center prospective randomized controlled study with a large sample reporting a decrease in the duration of MV, and a decrease in multiple system organ failure and improvements in the PaO₂/FiO₂ ratio. The data from the ARDS network has been released in preliminary form with the full study being available in the next several months for review. The data are encouraging for patients who meet the ARDS network protocol inclusion criteria, thus limiting the application to the general ARDS population. Low tidal volume ventilation trial by the ARDS network provides different overall outcome results compared to
several small studies (Amato et al., 1998; Stewart et al., 1998; Brochard, et al. 1998; & Brower et al., 1999), however the study design and sample size strengthen the conclusions for utilization of smaller tidal volumes.

ARDS is associated with a high mortality rate and management is limited to expensive supportive care. Before researchers and clinicians can work towards treatment and prevention of ARDS, the scope of the problem needs to be understood. With the AECC diagnostic criteria, researchers can discover the incidence of ALI and ARDS. These data are necessary to define the scope of the problem, identify inclusive high-risk groups, and develop positive predictive biophysical markers. Once researchers can understand and predict the development of ARDS, then researches can investigate preventative or proactive interventions to stop the progression of ALI to ARDS.
References


Table 1
American-European Consensus Conference Diagnostic Criteria of Acute Respiratory Distress Syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Timing</th>
<th>Oxygenation</th>
<th>Chest Radiograph</th>
<th>PAWP when measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lung Injury Criteria</td>
<td>Acute Onset</td>
<td>PaO2/FiO2 ≤ 300 mm Hg (regardless of PEEP)</td>
<td>Bilateral infiltrates seen on frontal chest radiograph</td>
<td>&lt;18 mm Hg or no clinical evidence of left atrial hypertension</td>
</tr>
<tr>
<td>Acute Respiratory Distress Syndrome Criteria</td>
<td>Acute Onset</td>
<td>PaO2/FiO2 ≤ 200 mm Hg (regardless of PEEP)</td>
<td>Bilateral infiltrates seen on frontal chest radiograph</td>
<td>&lt;18 mm Hg or no clinical evidence of left atrial hypertension</td>
</tr>
</tbody>
</table>

Recommended criteria for acute lung injury and acute respiratory distress syndrome from the American-European Consensus Conference on ARDS, 1992
Table 2: Lung Injury Score

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Roentgenogram score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Alveolar Consolidation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alveolar consolidation in one quadrant</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Alveolar consolidation in two quadrants</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Alveolar consolidation in three quadrants</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Alveolar consolidation in four quadrants</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hypoxemia Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 225-299</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 175-224</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 100-174</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 ≤ 100</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Respiratory system compliance score when ventilated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance ≥ 80</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Compliance 60-79</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Compliance 40-59</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Compliance 20-39</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Compliance ≤ 19</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>PEEP Score when ventilated (cm H2O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP ≤ 5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PEEP 6-8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PEEP 9-11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PEEP 12-14</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PEEP ≥ 15</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

The sum of each section is added and 4 divide the total. A score > 2.5 is diagnostic of ARDS.

Murray, Matthy, Luce, & Flick (1988). Permission to use has been requested.
### Table 3
Comparison of Incidence of ARDS

<table>
<thead>
<tr>
<th>Author and years of study</th>
<th>Study Location</th>
<th>Definition of ARDS</th>
<th>ARDS incidence</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Villar et al. January 1, 1983 to December 31, 1985 | Canary Islands | - PaO2/FiO2 < 150 for 24 hours  
- Bilateral pulmonary infiltrates  
- No evidence of left ventricular failure | 1.5-3.5 | A small population with fewer cases of multiple trauma or drug use. Overall mortality was 70% for ARDS |
| Lewandoski et al. October 1, 1991 to November 30, 1991 | Berlin Germany | - A lung injury score of >2.5 | 3.0 | Study was powered for respiratory failure. ARDS was a secondary data point. |
| Thomsen et al. January 1, 1989 to December 31, 1990 | Utah | - PaO2/PAO2 < .20  
- Bilateral lung infiltrates  
- No evidence of heart failure or a PCWP < 18  
- Total thoracic compliance < 50mV/cm | 4.8-8.3 | Prospective study Did not assess people under age of 17. The PaO2/PAO2 of .2 compares to a PaO2/FiO2 ratio of about 110 |
| Evans | San Francisco | - PaO2/FiO2 ratio < 150  
- Bilateral pulmonary infiltrates  
- PCWP < 18 or no evidence of elevated left atrial pressure. | 25 | This study only completed 4 months of a 1-year study. These data were only published in abstract form |
| Luhr et al. October 6, 1997 to November 30, 1997 | Sweden, Denmark, and Iceland | - PaO2/FiO2 ratio < 300 for ALI  
- PaO2/FiO2 ratio < 200 for ARDS  
- Bilateral pulmonary infiltrates  
- PCWP < 18 or no evidence of elevated left atrial pressure. | ALI: 17.9  
ARDS: 13.5 | This study also compared previous reports using the same criteria, and determined that if more severe criteria were used, the incidence of ARDS would have been similar to previous studies with about 3.0 cases |
| NIH task force | None | None | 71 | Was the first report of incidence of ARDS. |

∞ The incidence of ARDS is reflected per 100,000 population per year
Table 4
Comparison of Prone Position Research

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Onset of effects</th>
<th>Duration of Prone position</th>
<th>% of responders</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fridrich et al. (1996)</td>
<td>20</td>
<td>Immediately</td>
<td>20 hours</td>
<td>100%</td>
<td>11%</td>
</tr>
<tr>
<td>Vollman &amp; Bander (1996)</td>
<td>15</td>
<td>20 minutes</td>
<td>20 minutes</td>
<td>60%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chatte et al. (1997)</td>
<td>32</td>
<td>60 minutes</td>
<td>4 hours</td>
<td>78%</td>
<td>56%*</td>
</tr>
<tr>
<td>Pelosi et al. (1998)</td>
<td>16</td>
<td>30 minutes</td>
<td>2 hours</td>
<td>56%</td>
<td>43%</td>
</tr>
<tr>
<td>Jolliet et al. (1998)</td>
<td>19</td>
<td>30 minutes</td>
<td>12 hours</td>
<td>57%</td>
<td>79%◊</td>
</tr>
</tbody>
</table>

* Mortality was not related to the prone position, rather average death occurred 18 days after starting with prone cycles
◊ Protocol required a severe presentation of ARDS before admission to study.
Table 5: Comparison of Low Tidal Volume Ventilation Research

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Age Range</th>
<th>Definition of ARDS</th>
<th>Tidal Volumes</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato et al. 1998</td>
<td>53</td>
<td>14 - 70 years</td>
<td>• LIS &lt; 2.5, Clinical risk factors, PCWP &lt;16</td>
<td>PV: &lt;6cc/kg CV: 12cc/kg</td>
<td>PV: 38%</td>
<td>CV: 71% Improved status at 28 days, however mortality rates at discharge were insignificant.</td>
</tr>
<tr>
<td>Brower et al. 1998</td>
<td>52</td>
<td>&gt;18 years</td>
<td>• PaO2/FiO2 ≤ 200 torr, Radiographic findings, No evidence of heart failure, PCWP &lt; 18</td>
<td>PV: 8cc/kg CV: 10-12 cc/kg</td>
<td>PV: 50%</td>
<td>CV: 46% Failed to demonstrate an improvement in mortality rates. There were no differences in complications between the two groups. Protective ventilation appeared to be as safe as conventional therapy</td>
</tr>
<tr>
<td>Stewart et al. 1998</td>
<td>120</td>
<td>&gt;18 years</td>
<td>• PaO2/FiO2 &lt; 250, Presence of identified risk group</td>
<td>PV: 8cc/kg CV: 10 – 15 cc/kg</td>
<td>PV: 50%</td>
<td>CV: 47% Reported improved results at 28 days, however, improvement in overall mortality was not significant</td>
</tr>
<tr>
<td>Brochard et al. 1999</td>
<td>116</td>
<td>&gt;17 years to &lt; 76 years of age</td>
<td>• Bilateral radiographic infiltrates, Required ventilation with &gt;.50 FiO2 for hypoxia for &gt; 24 hours, LIS &gt; 2.5 for &lt; 72 hours</td>
<td>PV: 6-10 cc/kg CV: 10 – 15 cc/kg</td>
<td>PV: 46%</td>
<td>CV: 37% Stopped early because initial evaluation of data failed to demonstrate an improvement in overall mortality. There were no significant differences in ventilator complications</td>
</tr>
<tr>
<td>ARDS Network Group 2000</td>
<td>861</td>
<td>&gt;17 years of age</td>
<td>• PaO2/FiO2 ratio &lt;300, Bilateral pulmonary infiltrates on x-ray, A PCWP &lt;18 or no clinical evidence of Left atrial hypertension</td>
<td>PV: 4-6 cc/kg CV: 12 cc/kg</td>
<td>PV: 31%</td>
<td>CV: 40% A large multi-center study. Demonstrated a decrease in mortality, an increase in ventilator free days, and a decrease in multiple organ failure.</td>
</tr>
</tbody>
</table>

PV = Protective ventilation  
CV = Conventional ventilation