New Perspectives on Adult Respiratory Distress Syndrome

Dr. Cevher Özcan[1], Dr. H. Canan Hasanoğlu[2], Dr. Zeki Yıldırım[2]

The Adult Respiratory Distress Syndrome (ARDS) is sudden onset of respiratory failure charecterized by diffuse infiltrates on the chest radiography, severe hypoxsemia, and diminished pulmonary compliance. Pathologic features included severe pulmonary edema, vascular congestion with hemorrhage, atelectasis, and hyaline membrane formation. The incidance of ARDS is approximately 75 cases per 100 000 each year in United States. As our knowledge of the clinical and epidemiologic features of ARDS has progressed, our understanding of the cellular and molecular mechanism leading to the production of lung injury became more clear. The pathogenesis is a complex series of inflammatory events, including participitation of performed plasma derivated inflammatory mediators. Management of the patient with ARDS is complex, particularly because the condition frequently occurs in the setting of multiple organ disorders syndrome (MODS). General management principles include diagnosis and treatment of the underlying cause of ARDS, cardiopulmonary and nutritional support and avoidance from the treatment complications. [Journal of Turgut Özal Medical Center 1997;4(3):360-369]

Key Words: *ARDS, inflammatory mediators, therapy, pathophysiology*

Erişkin solunum zorluğu sendromunda yeni görüşler

Erişkin solunum zorluğu sendromu (ARDS); göğüs grafisinde yaygın infiltrasyonlar, şiddetli hipoksemi ve akciğer kompliansında azalma ile karakterize solunum yetmezliğinin ani başlasıdır. Patolojik özellikleri; şiddetli akciğer ödemi, damarlar kan birikmesi ile genişleme, atelektazi ve hyalen membran oluşumunu içerir. ARDS sıklığı Birleşek Devletler'de her yıl yaklaşık 100000'de 75 vakadır. ARDS'nin klinik ve epidemiyolojik özellikleri hakkındaki bilgilerimiz, akciğerde zedelenmeye yol açan hücresel ve moleküler mekanizmaların daha açık olarak anlaşılması ile birlikte gelişmiştir. Patolojisi, inflamatuar mediatörlerin plazma ürünlerinin yaptıkları katılımlarıda içeren inflamatuar olayların karmaşık bir seyridir. ARDS'li hastaların tedavisi zordur, özelliklede sık raslanan bir durum olması dolayısıyla, yaygın organ bozukluğu sendromu (MODS) toblosunun oluştuğu hallarde. Genel tedavi kuralı ise: ARDS'nin altta yatan nedeninin tanısı ve tedavisi, kalp-akciğer ve beslenme desteği ve tedavi komplikasyonlarından kaçınmadır. [Turgut Özal Tıp Merkezi Dergisi 1997;4(3):360-369]

Anahtar Kelimeler: *ARDS, inflamatuar mediatörler, tedavi, patofizyoloji*

ARDS has been evolving since the initial descriptions of the disorder by Ashbaugh and colleagues in 1967. At first, the syndrome was defined by pulmonary phsiologic parameters. Abnormal pulmonary microvascular permability coefficients resulting in lung edema and abnormal regulation of ventilation-perfusion matching resulting in hypoxemia in the lung were considered necessary and sufficient phsiologic hallmarks. ARDS is a discriptive term that has been applied to many acute, diffuse infiltrative

1 İnönü University, School of Medicine, Departments of Internal Medicine, Malatya
2 İnönü University, School of Medicine, Departments of Pulmonary Medicine, Malatya

lung lesions of diverse etiologies when they are accompanied by severe arterial hypoksemia.The extrapulmonary abnormalities were accompanied pulmonary disfunction during ARDS that included hepatic disfunction, renal disfunction, altered mental status, coagulopathies, gastrointestinal bleeding and dysmotility, and a propensity for superinfection. Presence of infection and extrapulmonary multiple organ disfunction syndrome (MODS) emerged as the most important predictors of mortality in ARDS patients. Accordingly, respiratory failure caused by ARDS is now commonly viewed as a part of multisystem disorder (1). In the neonatal form, immaturity of alveolar surfactant production and increased compliance are primarily involved in the pathophisiology, whereas in the adult, alveolar surfactant changes are secondary to the primary process, and the chest wall is not compliant (2).

Following trauma, shock, sepsis, aspiration, or a variety of other direct or indirect pulmonary insults, a number of patients develop progressive respiratory distress charecterised by 1- tachypnea, dyspnea, cough, and the physical findings of airspace consolidations; 2- diffuse airspace disease on chest roentgenography; 3- severe arterial desaturation that is resistant to even high concentrations of inhalet oxygen; and 4- pulmonary function evidence of increased pulmonary vascular pressure, resistance and decreased lung compliance (3,4).

EPIDEMIOLOGY AND CLINICAL PREDISPOSITIONS

ARDS, a process of non-hydrostatic pulmonary edema and hypoxemia associated with a variety of etiologies carries a high morbidity (10-90) and financial cost. The reported annual incidence in the United States is 150,000 cases, but this figure has been challenged and may be different in Türkiye. The reason is the heterogenity of diseases underlying ARDS and the lack of uniform definitions for ARDS. The true incidence and outcome on this clinical syndrome is impossible.

Presently; there is a growing population of immunocompromised hosts, arising from use of agressive antitumor chemotherapy, from the growing popularity of organ transplantation, and from the spread of the acquired immunodeficiency syndrome (ARDS). These factors may be shifting the epidemiology of ARDS toward primary pulmonary infection in immunocompromised hosts. A partial listing of these causes in shown in Table 1 (5, 6). In 1988, Murray and coleagues proposed lung injury be graded to judge the extent of respiratory impairment in the setting of ARDS by devoloping a lung injury score (Table 2) (7). Using this quantitative, objective approach to assess the severty of lung injury, the course and response the therapy could be studied carefully.To date, however, most published clinical studies have failed to clearly identify underlying diseases that are present in ARDS patients (8).

Tablo 1. Conditions which may lead to the ARDS

1. Diffuse pulmonary infections: e.g., viral, bacterial, fungal, pneumocystis, milliary tuberculosis.
2. Aspiration: e.g., gastric contents with Mendelson's Syndrome, water with near drowing.
3. Inhalation of toxins and irritans: e.g., clorine gas, NO_2, smoke, ozone, high concentration of oxygen, phosgene.
4. Narcotic overdose pulmonary edema: e.g., heroin, methadone, morphine, dextropropoxyphene.
5. Nonnarcotic drug effect: e.g., ethchlorvynol, salicylate, nitrofurantoin, tricyclic, paracuat, bleomycin.
6. Immunologic response to host antigens: e.g., Goodpasteur's syndrome, Systemic Lupus Erythematosus.
7. Effects of nonthoracic trauma with hypotention, major surgery or extensive trauma
8. In association with systemic reactions to processes initiated outside the lung(e.g., gram-negative and staphylococal septicemia, hemorrhagic pancreatitis, amniotic fluid embolism, fat embolism), eclampsia, DIC
9. Post cardiopulmonary bypass: e.g., pump lung, postperfusion lung.
10. Massive multiple transfusions.
11. Burns, skletal fractures.
12. Hemodialysis and renal failure
13. Cerebral injury

Instead, physiologic criteria have been relied upon exclusively in many published clinical series.

Worldwide, the most common cause of ARDS is propably trauma. ARDS is a leading cause of subsequent mortality. In civilian settings, the sepsis syndrome (fever, hypotension, and leukocytosis or leukopenia) is the leading factor that predisposes patients to ARDS (9). The likelyhood of developing ARDS increases if more than one of the risk factors is present (5).

Tablo 2. Components and individual values of the lung injury score

Chest roentgenogram score		Value
No alveolar consolidation		0
Alveolar consolidation confined		
to 1 quadrant		1
to 2 quadrants		2
to 3 quadrants		3
to 4 quadrants		4
Hypoxemia score	Range	Value
PaO_2/F_{IO2}	≥300	0
PaO_2/F_{IO2}	225-299	1
PaO_2/F_{IO2}	175-224	2
PaO_2/F_{IO2}	100-174	3
$PaO_2/F_{IO}2$	≤100	4
PEEP score (when ventilated)	Range	Value
PEEP	5 cm H_2O	0
PEEP	6-8 cm H_2O	1
PEEP	9-11 cm H_2O	2
PEEP	12-14 cm H_2O	3
PEEP	15 cm H_2O	4
Respiratory sys compl score	Range	Value
Compliance	≥80 ml/cm H_2O	0
Compliance	60-79 ml/cm H_2O	1
Compliance	40-59 ml/cm H_2O	2
Compliance	20-30 ml/cm H_2O	3
Compliance	≤19 ml/cm H_2O	4
Final value score		
No lung injury		0
Mild to moderate lung injury		0.1-2.5
Severe lung injury (ARDS)		2.5

CLINICAL CHARACTERISTICS, SINGS, AND SYMPTOMS

Clinical manifestations can develop either insidiously, haurs or days after the initiating event or acutely, coincident with the event. Typical symptoms are dyspnea, tachypnea, dry cough, retrosternal discomfort, and agitation: cyanosis may be present. Examination of the chest reveals fine cracles and bronchial breath sounds. These physical findings may be obscured during assisted mechanical ventilation (10). The diagnosis is confirmed in an appropiate clinical setting by demostrating hypoxemia and x-ray evidence of pulmonary edema without clinical evidence of congestive heart failure (10). However, at the time of initial injury and for several hours there after the patient may be free of respiratory symptoms or sings. Physical examination may be unremarkable, although a few fine inspiratory rales may be audible. Radiographically the lung fields may be clear or demostrate only minimal and scattered interstitial infiltrates. With progression, the patient becomes cyanotic, dyspneic and tachypneic. Rales may become more prominent and easly heard throughout both lung fields along with regions of tubuler breath sounds; the chest radiograph demostrates diffuse, extensive bilateral interstitial and alveoler infiltrates. With further progression, and if mecanical ventilator and PEEP therapy are delayed, the combination of increasing tachypnea and decreasing tidal volumes result in alveolar hypoventilation, with increase in PCO_2 levels and worsening hypoxemia

In conclusion, the physiologic hallmarks that are characteristic of the disorder are : **a-**Alveolar and/or interstitial infiltrates on chest x-ray in the absence of evidence of congestive heart failure; **b-**Severe hypoxemia that persist when breathing oxygen-enriched air (Arterial/alveolar oxygen ratio<0,3). **c** - Decreased lung compliance (Total throracic static compliance<40ml/cm$H_2$0) **d-**Decreased functional residual capacity; and **e-**Increased pulmonary vascular resistance (Pulmonary capillary wedge pressure <18 mmHg) (11). Arterial blood analysis shows severe hypoxemia and a normal or decreased $PaCO_2$. The hypoxemia is difficult or impossible to correct even with the use of very high concentrations of inspired oxygen. Clinical deterioration is usualy requaring endothracheal intubation to maintain oxygen saturation greather than 90 per cent. The most important pathophysiologic effect of the edema in patient with ARDS is on gas exchance, profund hypoxemia rather than ventilatory failure being the major indication for intubation and mechanical ventilation. The hypoxemia is caused by intrapulmonary shunting of blood through edematous lung regions (12). The intrapulmonary shunt in patients with ARDS increases when total pulmonary blood flow is increased, an effect that is probably related to an increase in mixed venous PO_2 and decreased hypoxic vasoconstriction (13). ARDS is often accompanied by pulmonary arterial hypertansion, increase in right ventricular afterload and right ventricular dysfunction (14). There is also evidence that right ventricular dysfunction can result in left ventricular dysfunction, most likely related to a shift in the shared intraventricular septum. The progression or regression of pulmonary edema in ARDS can be followed using serial chest roentgenograms, serial studies of gas exchange.

PATHOGENESIS AND CELLULAR MORPHOLOGY

The pathophysiology of ARDS remains obscure, but is the subject of ongoing reseach. Innitialy, investigations of the pathophysiology of ARDS were focused upon the etiology of the pulmonary edema or altered alveolar permeability that directly followed defined injurious interventions (15). There appears to be little correlation between the amount of edema fluid present and the severity of gas exchange dysfunction in patients with ARDS. Also careful morphologic studies of the lungs of patients biopsied during ARDS or examined after death showed that there is much more to ARDS than edema. There is a complex derangement of lung structure and function that includes all architectural structures of the lung. Morphologically, the evalution of ARDS can be divided for convenience in to the three phases (16);

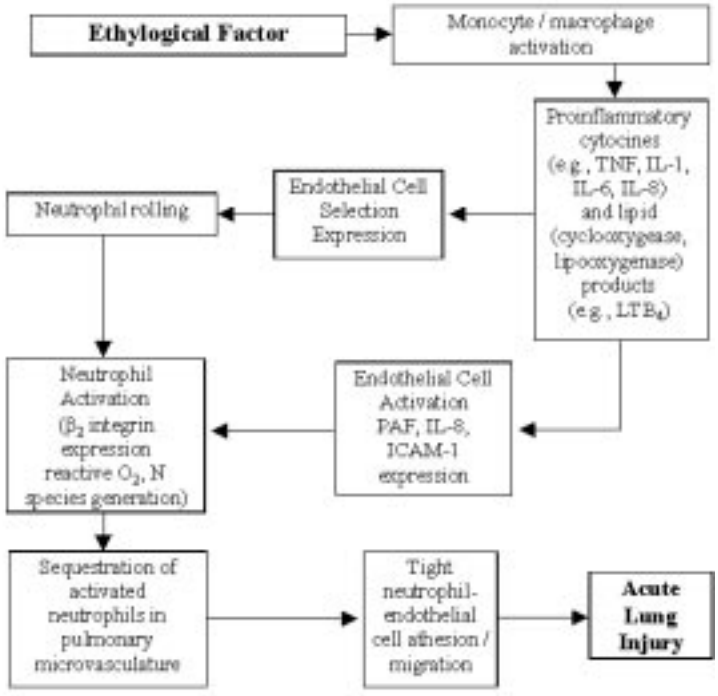

Figure 1. The steps detailed describe a likely mechanism that leads to acute lung injury.

1-Injury phase; alveolar capillary and epithelial injury, increased permability and edema.

2-Reporative/Proliferative phase; Type 2 epithelial cell regenaration: interstitial inflammation with granulocytes and mononuclear cells.

3-Fibrotic phase; interstitial collagen accumulation and architectural obliteration.

Grossly, the lung are heavy, edematous, and nearly airless with region of hemorrhage, atelectasis and consolidation. By light microscopy there is edema, and cellular infiltration of interalveolar septa and interstitial spaces surrounding airways and blood vessels, atelectasis and hyalen membranes in many regions, engargement of vessels with red blood cells, and aggregates of platelets and polymorphonuclear leukocytes (PMNL) along with interstitial and alveolar hemorrhage. In addition, both hyperplasia and dysplasia of the granuler (Type 2) pneumocytes are often present (17). If the illness has been prolonged beyand 10 days, significant interstitial fibrosis and emphysematous changes may be found in the lung.

The pathogenesis involves a complex series of inflammatory events, inclueding participation of performed plasma-deriveted inflammatory mediators and newly generated arachidonic acid mediators from both the cyclooxygenase and the lipoxygenase pathways (Figure 1). Activation of the complement and blood clotting systems can also be involved, in addition to recruitment of numerous inflammatory cell types.

Shock: in experimental studies, prolonged hypotension can result in both pulmonary endothelial damage and increased microvascular permeability (18, 19). But it is difficult to cause ARDS by shock alone, and it is probable that other factors are involved in producing the complete syndrome.

PMNL: experimental and clinical studies provide strong support for the important contribution that neutrophils make to the pulmonary damage in ARDS, there is also convincing that the syndrome can occur in the absence of circulating or tissue neutrophils (20). Animal models of acute lung injury that are dependent on the presence of neutrophils. The presence of numerous neutrophils in some biopsy and postmortem lung specimens from patients with established ARDS (21). Animal models in which chemotactic agents such as C5a have been shown to attract leukocytes to the

pulmonary microvasculature with resulting pulmonary microvascular injury. Neutrophils can be activated by a variety of mechanisms. Resulting in penetration of the cells through junctions between endothelial cell as well as the genaration and release of oxygen free radicals, lysosomal enzymes, and arachidonate metabolites (22). Many reports indicated these products of activated neutrophils have the capacity to damage the capillary endothelium and the alveolar epithelium.

Surfactant: Its deficiency, either primary or secondary, will cause significant in the normal lung suggest that surfactant deficiency result in many of the physiologic changes in ARDS. Surfactant levels and composition are also abnormal in patients with ARDS. There are at least two major mechanisms of surfactant abnormalities in ARDS; 1- Type 2 cell injury and protein inactivation of surfactant (23), Figure 2 shows; simplified pathophysiologic sequance of events influencing surfactant in ARDS. In fact, distribution of surfactant by itself can increase lung water, presumbably by increasing the surface tension at the alveolar fluid-air interface, resulting in the passage of water from the interstitial space (24).

Complement: The blood and BAL fluid of patients who have ARDS have been shown to contain increased levels of activated complement components (25).

Clotting systems: There is considerable evidence to suggest that activation of the blood clotting system is associated with ARDS (26). Patients with estanblished ARDS frequently have elevated blood levels of fibrin degradation products. In experimental animals, activation of the clotting system is associated with increased microvascular permability and the development of pulmonary edema (1).

Oxygen free radicals can demage the lung by denaturation of lipids associated with the plasma membrane, by inactivation of sulfhydryl-containing protein enzymes and by depolymerization of polysaccharides. Their toxicity is enhanced by hyperoxic conditions and decreased by hypoxic conditions. Clinical evidence for the presence of oxygen metabolites in ARDS includes the finding of increased levels of H_2O_2 in the breath of ARDS patients compared to control subjects. Increased levels of oxidized antiproteases are present in the lung lavages of patients with ARDS compared to controls. There is both clinical and experimental evidence to support the role of activated neutrophils and the enzyme xanthine oxidase as specific sources of oxygen radicals in the causation or amplification of acute lung injury (3).

Inflammatory enzymes and mediators: Models of acute lung injury leading to the development of ARDS use provocative stimuli such as endotoxin,

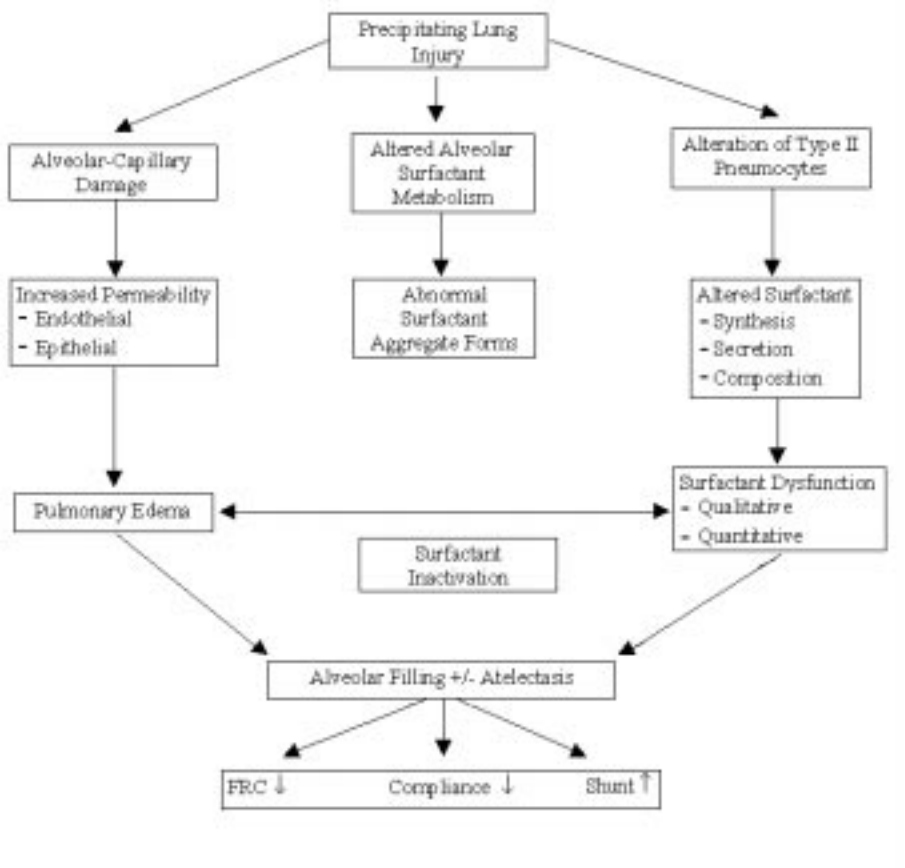

Figure 2. Pathophysiology of surfactant.

thrombin, complement, platelet-activating factor (PAF), and arachidonate metabolites (27). TNF-alfa and interleukine-1(IL) appear to be central to the diverse processes leading to endothelial injury. IL-1 in turn induces endothelial biosynthesis of both arachidonate metabolites and PAF, that have the ability to initiate lung injury. Cytocines effect on granulocyte adherence to endothelial surfaces may explain the rapid margination phenomenon. Cytokines induce surface expression of an antigen, the endothelial leukocyte adhesion molecule, or ELAM (27) ELAM also augments endothelial surface procoagulant activity. TNF-alfa also stimulates angiogenesis and neovascularization, IL-1 can enhance superoxide anion release from cultured endothelial cells.

Thromboxane causes platelet aggregation and pulmonary vascular constriction, whereas prostacyclin is a potent pulmonary arterial dilator and is capable of causing disaggregation of platelets. The leukotrienes can cause edema. Although plasma levels of prostoglandins are not increased in patients with ARDS, increased levels of leukotrienes have been identified in the edema fluid of such patients (1). There is also evidence for decreased pulmonary removel of certain prostoglandins(PG), such as PGE1, probably secondary to the diffuse endothelial injury that constitutes the basic features of ARDS. There is some evidence for precallicrein activation in the blood and BAL fluid of patients with ARDS (3). Bradykinin, elastase and other neutrophil derived enziiymes can be detected in the blood and BAL fluid of patients with ARDS. Increased levels of the enzyme phospholipase A2 have been demostrated in ARDS. If the phospholipase gained access to the alveolar compartment, it could cause degradation of surfactant and thus contribute to decreased lung compliance characteristic of ARDS (23).

MANAGEMENT

During the post 20 years many attempts have been made to reastablish normal ventilation-perfusion relationships pharmocologic manupulation of pulmonary circulation. Since no single therapy has been demostrated to reduce mortality the reason for this apparent reduction in mortality remains unexplanied. Many new therapies have been proposed in the last several years in the both the supportive and definitive aspects of treatment. (Table 3) (28).

The therapy of ARDS is supportive. The goals of supportive care are diagnosis and therapy of underlying (predispositions) pathology, minimizing accumulating pulmonary edema fluid without compromising renal function, minimizing oxygen toxicity, nutritional support and minimization of the duration and iatrogenic complications of invasive life support.

The mechanical ventilatory support opens previously closed airways and improving oxygenation. This is accomplished by using large tidal volumes (approximately 10 to 15 ml per kilogram of lean body weight) at a slower breathing rate (12 to 15 breaths per minute) than the spontaneous one of patient. The ventilatory mode, FIO_2 PEEP, tidal volume, ventilatory rate are adjusted to provide optimal gas exchange. PEEP then may be increased in increaments of 3 to 5 cmH_2O, guide by oxygenation and clinical or hemodynamic parameters related to PO_2. The most

Tablo 3. Therapies for ARDS

- A- Supportive treatment:
  - 1- Mechanical ventilation
    - a- Assist/control volume-limited ventilation
    - b- Intermittent mandatory ventilation
    - c- Inverse ration ventilation
    - d- High frequency ventilation
    - e- Airway pressure release ventilation
    - f- Permissive hypercapnia
  - 2- Nonventilator non pharmocologic gas exchange support methods
    - a- Extracorporeal membrane oxygenation
    - b- Intravenous oxygenator
    - c- Prone position
    - d- Liquid ventilation using liquid perfluorocarbon
  - 3- Fluid and hemodynamic management continuous arteriovenous hemofiltration
  - 4- New pharmacologic supportive therapies
    - a- Almitrine
    - b- Nitric oxide
    - c- Surfactant replacement.
- B- Deffinitive therapy to interrupt mechanisms of inflammation and injury
  - 1- General agents to inhibit inflammation
    - a- Corticosteroid
    - b- Prostaglandin E_1
    - c- Ketoconazole
    - d- Ibuprofen
    - e- Pentoxifylline
    - f- Fibronectin
  - 2- Specific agents to inhibit inflammation
    - a- Antiendotoxin therapies
    - b- Anticytokine therapies
    - c- Antioxidants
    - d- Anticomplement therapy
    - e- Antiprotease therapy

common modes of ventilation used in conventional management of patients with ARDS include assist/control volume limited ventilation and intermittent mandatory ventilation. Pressure-controlled ventilation is often used inverse ratio ventilation (IRV) or permissive hypercapnia is carried out. IRV consists of progressively prolonging the inspratory time, holding the lungs at peak inflation(29). IRV could be recruting previously unventilated areas alveoli related to the prolongation of inspration. Currently, IRV is usually reserved as a so-called salvage from of therapy, applied in the circumstance in which conventiolal ventilatory management is failled.

High frequency ventilation and airway pressure release ventilation have been suggested for use in patients with ARDS. But, no adventage was found when compared with conventional mechanical ventilation (30,31). A relative new concept of the goals of so-called permissive hypercapnia are to ventilate the patient with a lower tidal volume an lower plateau pressure (32). A resent study comparing two tidal volumes in patients with ARDS, which found a significant improvement in oxygenation at the higher tidal volum suggesting recruitment during the inspiratory phase (33).

Some methods for improving oxygenation and CO_2 removal have been proposed for ARDS. These methods include both extracorporeal and intra vascular gas exchance devices, and prone positioning of the patient (28). Extracorporeal membrane oxygenation reported in 1979 that has not been considered a standard therapy for ARDS because, mortality for this therapy was unchanged compared with the control group (34). An intravenous oxygenator has been proposed as a pulmonary assist device for improving gas exchance in patients with severe acute respiratory failure (35). Turning patients with ARDS from the supine to the prone position has been suggested for some time as a maneuer that will improve oxygenation in these patients (36). Published experience with liquid ventilation using liquid perflourocarbon in humans is limited. But it has been proposed both for infant and adult ARDS which has an advantage for facilitating lung expansion compared with air ventilation in a surfactant deficient lung (37).

Three relative new pharmacologic therapies proposed for patients with ARDS can be considered to be supportive therapy. These consist of intravenous administration of Almitrine, inhalation of nitric oxide (NO) and intrabronchial administration of surfactant. Almitrine can enhance hypoxic pulmonary vasocostriction and increase ventilatory drive and when administered to patient with ARDS, there is a clear improvement in arterial oxygenation shortly after its intravenous administration (38). NO is an inflammatory mediator with cytotoxic potential, a bronchodilator and potent pulmonary vasodilator. Vasodilation occurs in the ventilated areas, blood is diverted from the poorly or nonventilated areas to better ventilated areas of lung and improvement in ventilatio/perfusion matching and reduction in intrapulmonary shunt occurs. If the improvement in arterial oxygenation allows a reduction in fractional inhaleted oxygen to the extend that potential pulmonary oxygen toxicity can be avoided or reduced, one might expect a significant improvement in survival or intensive care unit lenght of stay. NO inhalation may fail to improve pulmonary gas exchance or to reduce pulmonary hypertention in patients with severe ARDS (39). In addition: the effects of intravenous almitrine and inhaled NO can be additive(40). Surfactant replacement has been shown to be benifical, including improvement in survival when administered to neonates with infant respratory distress syndrome. Possitive effects of exogenous surfactant administration on acute lung injury have been reported to adults. There now a prospective, randomized clinical trial evaluating the efficacy of aerosolized exogenous surfactant in patients with ARDS. Some trial have demostrated improvement in gas exchance and a trent toward decreased mortality in response to the surfactant. Despite these encouraging results, there are multiple factors requiring further investigation in the development of optimal surfactant treatment strategies for patients with ARDS (41). Surfactant is a viscous substance and presumably in order to be effective must reach the terminal bronchioles and/or alveolar spaces. Whether this can best be accomblished by nebulization or by intrathracheal installation with subsequent position of the patient to enhance a diffuse distribution is not known (28,41).

General agents to inhibit inflammation are Corticosteroid, Prostoglandin E_1 (PGE_1), Ketoconazole, Ibuprofen, Pentoxifylline, Fibronectin. Corticosteroid in the form of methylprednisolone intravenously is the drug most widely studied in early ARDS. All the trials gave either 1 or 2 days of high-dose intravenous methylprednisolone. Results of all of the trials were essentialy negative with no evidence

for either ARDS prevention or improved mortality once ARDS was present. Even, some studies found evidence of increased secondary bacterial or fungal infection in the steroid treated group (4,42).

Prostoglandin E_1 was effective in reducing pulmonary arteria pressures and improving cardiac output in patients with ARDS and pulmonary hypertention. It has been suggested that the failure to find a benificial effect with PGE_1 may have been due to the failure of the drug to reach the sites required for an active effect. But the randomized trial failed to confirm any survival benifit of PGE_1 (43).

Ketoconazole has been shown to be a potent specific inhibitor of thromboxane and 5-lipoxygenase and also inhibits procoagulant activity. Two prospective randomised placebo controlled trials in patients at high risk for ARDS showed a significant reduction in mortality and to found a significant reduction in the incidence of ARDS (44).

Ibuprofen, has been effective in animal models, including those of sepsis, both of pretreatment and to a lesser extend, posttreatment protocols. One study showed a trend toward an increased rate of shock reversal and a significant decrease in temperature, heart rate, and peak airway pressure with ıbuprofen compared with placebo (45).

Pentoxifyline has several possible effects, including inhibition of chemotoxis and activation of neutrophils in animal models of sepsis. No efficient data are avaliable in human. Fibronectine is an opsonin that is known to be decreased in critically ill patients. Two studies of fibronectin replacement in patients with sepsis, one of cryoprecipitate administration and the other using purified fibronectin failed to demonstrate improvement in mortality or other outcome variables (46).

Antiendotoxin therapies are consist of polyclonal and monoclonal antibody. Preparation and use of the polyclonal antibody was not practical. Two monoclonal antibodies against endotoxin HAIA and E_5, have been involved in a series of studies. Two antibodies are a significant increase in survival of patients with gram negative bacteriemia but no overall improved mortality for the patients with sepsis entered into the study (28).

Tumor necrosis factor-alpha(TNF-α) and interleukin-1(IL-1) are two cytokines to be most important in this process. Several approaches to inhibitting these cytokines have been considered and some of these have been subjected to clinical trials. The variable correlation of TNF-α levels and outcome the experimental finding that in most studies, the TNF-α antibody had to be administred before a bacterial or endotoxine challenge in order to be effective, and the experimental finding that even when benifical, TNF-α monoclonal antibodies do not totally eliminate the effects of endotoxins (47). A recombinant form of IL-1 receptor antogonist has been studied. A subsequent large phase 3 randomized plasebo controlled trial of 893 patients with sepsis failed to find significant differances in mortality between the placebo group and the two doses of receptor antagonist studied. In addition, a retrospective analysis based on a risk prediction model for death from sepsis suggested possible survival benifit from IL-1receptor antagonist (48).

N-acetylcystein has been studied as a source of glutathione which then acts as an oxygen radical scavenger. No improvement in oxygenation was found. A trend toword improve total chest compliance was seen in the treatment group but was not statistically significant, and no survival difference was found (49).

Anticomplement therapy have been performed. Phase 2 trials of treatment with high doses of intravenously administered C-1 inhibitor. There is an active effect an attenuating complement activity in septic shock (46).

Antiprotease therapy has been proposed to limit the development of or even treat ARDS since proteases like oxygen radicals are also released by activated neutrophils in the lungs and other organs. Platelet activating factor (PAF) antagonists have been proposed as possible therapy. Antibodies against adhesion molecules have been developed to transiently prevent neutrophil adherence to endothelium. Varius means of inhibiting activation of coagulation including antiprocoagulant agents have been proposed as possible therapy(28).

Supportive care for pattients with ARDS has evolved since 1967. However, no statistical improvement in clinical outcome has been demostrated. The published mortality of ARDS has remainded between 50% and 70% in several recent studies as it was in 1971 (50). If all recently published series are taken together, the mortality rate is between 50 and 60 percent. Epidemiologic factors such as

immunosupression and the avilability of organ transplantation may have shifted the clinical spectrum of patients who meet ARDS criteria toward immunocompromised patients or those with irrevesible underlying disease. In survivors with previously normal lung function, the long term prognosis for recovery appears to be remakably good. Infection and MODS are significant factors, producing morbidity and mortality in many patients during the course of ARDS. Other clinical factors for mortality in ARDS include persistant acidosis, thrombocytopenia, advanced age, premorbit conditions, persistant BAL neutrophilia, and persistantly impaired oxygenation. If the patients survive the fibrosis, lung volumes and arterial blood gases have been shown to return to normal levels within 4 to 6 months after respiratory failure.

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Correspondence Address:
Cevher ÖZCAN, MD
İnönü University, School of Medicine
Department of Internal Medicine
Turgut Özal Medical Center
44069 MALATYA
Fax: 422- 3410728