

## Round Table Conference Acute Lung Injury

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### INTRODUCTION

Thirty investigators convened in Brussels for a three-day series of presentations and discussions sponsored by the European Society of Intensive Care Medicine and the American Thoracic Society. The aims of the meeting were to integrate basic scientific and clinical knowledge in the field of acute lung injury (ALI), to underline persistent problems, and thereby to identify the essential topics for future research. Detailed, referenced reviews of each topic discussed in this forum, incorporating descriptions of research questions of current interest, have been collected in monograph form (1). This report provides an overview of the conference proceedings.

### EPIDEMIOLOGY OF ACUTE LUNG INJURY

In adults, lung injury may complicate a wide range of serious medical and surgical conditions, only some of which involve a direct pulmonary insult. Although the extreme form of acute lung injury, acute respiratory distress syndrome (ARDS), was first described formally some 30 years ago, a uniformly accepted clinical definition was not published until 1994. Simultaneously, ALI was defined as a distinct clinical entity in recognition of the spectrum of severity of pulmonary damage that may occur in association with the wide variety of precipitating conditions. ALI and ARDS are distinguished only by the severity of the refractory hypoxemia that characterizes both conditions, a distinction that may prove to have little clinical relevance. Nevertheless, in terms of recognizing the incidence, epidemiology, and histopathologic evolution of lung injury and in carrying out trials of therapeutic interventions, the distinction is important. The overall incidence of ARDS remains unclear, but most studies suggest a rate of approximately 2-8 cases per 100,000 population per year. Similar data for ALI are unavailable. The incidence and mortality associated with ARDS depend in part upon the underlying risk factor(s). Moreover, such epidemiologic data are definition-dependent, and as already noted, the latter has not been standardized until recently. However, the clinical course seems variable, the mean duration of mechanical ventilation being 10-14 d, while 10-20% of patients remain ventilator-dependent for longer than 3 wk. Duration of mechanical ventilation is inversely correlated with mortality, in that patients alive but dependent upon such support after 3 wk have a high survival rate. Until recently, the fatality rate of ARDS was considered to exceed 50%. Mortality is higher in patients over 60 yr and in those with sepsis. Other factors associated with mortality

are the severity of underlying illness, as characterized by the injury severity score in trauma patients, or the presence or development of multiple organ failure. While the initial severity of lung injury quantified in terms of  $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$  ratio does not predict outcome, improvement in such indices over the first 3 d to 1 wk is associated with increased survival. Recent analyses of temporal trends in a single institution suggest a decline in ARDS fatality rates between 1990 and 1993. This observation has been most notable in patients with ARDS associated with sepsis and in patients under 60 yr of age. In the absence of new and definitive therapeutic interventions, it seems that this trend must be attributed to improved supportive therapy. Epidemiologic studies suggest that fewer than 20% of nonsurviving patients with ARDS die from refractory hypoxemia; the majority succumb to nonrespiratory causes. Multivariate analysis of European data suggests that age, pre-existing disease, and APACHE III score correlate with survival. Importantly, an initial favorable response of the patient to supportive interventions is also an indicator.

### PATHOPHYSIOLOGY

#### Basic Mechanisms

In recent years, investigations into increased alveolar capillary permeability in ARDS have centered upon the neutrophil, the macrophage, and the pulmonary vascular endothelium. Neutrophil sequestration and migration within the lung remain histologic hallmarks of ARDS and result both from chemotactic stimuli released within the lung and the activation of neutrophils by circulating mediators. Most experimental models of ARDS have used lipopolysaccharide (LPS) to trigger inflammatory responses by interacting with specific host proteins that initiate cytokine production. During acute phase responses, a plasma protein that binds endotoxin, lipopolysaccharide-binding protein (LBP), has been identified. LBP enhances several LPS-stimulated responses that could contribute to ARDS, including the regulation of CD18, the adherence of neutrophils to endothelium, and the production of cytokines (e.g., tumor necrosis factor alpha [TNF- $\alpha$ ] from alveolar macrophages). Secondly, the LPS/LBP complex interacts with CD14 to trigger intracellular responses and the development of lung injury. Significantly, increased levels of LBP and CD14 have been identified in bronchoalveolar lavage (BAL) fluid from patients with ARDS, the latter being strongly related to total protein and polymorphonuclear neutrophil concentrations, markers of increased alveolar-capillary membrane permeability and inflammation, respectively. The process that leads to the accumulation of neutrophils within the alveolar spaces includes recruitment to and retention of these cells within the lung. In the systemic circulation, endotoxin activates complement, and both primes and stimulates neutrophils and monocytes. Priming of neutrophils followed by stimulation with complement fragments could contribute to the development

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of clinical lung injury. However, whether circulating neutrophils in patients at risk for or with fully developed ALI or ARDS are primed or activated is currently unclear.

Significantly, LPS can also induce tolerance to inflammatory insults. Exposure to a sublethal dose of LPS is associated with relative hyporesponsiveness to subsequent exposure. The extent to which endotoxin tolerance could modulate the development of ARDS in individuals at risk remains unclear but represents an exciting therapeutic prospect. Finally, although LPS is implicated as an important agent in the induction of ARDS and is present in the plasma of many patients with sepsis complicated by lung injury, its precise source remains unknown. Translocation from the lumen of the gastrointestinal tract (see right ventricular failure below) is a possible mechanism; however, although endotoxin is detectable in the plasma of 42% of patients undergoing cardiopulmonary bypass when a measurable increase in gastrointestinal tract permeability is apparent, there is no evidence of a relationship between its severity and the level of endotoxemia.

Despite the high expectations of clinical trials of anti-endotoxin therapy, these have failed to demonstrate benefit in patients with sepsis. This failure may partly reflect the fact that LPS leads to the release of cytokines, which modulate its pro-inflammatory effects. The synthesis of TNF- $\alpha$  followed by the generation of interleukin (IL)-1 and IL-8 is detectable in the earliest stages of ARDS. The local release of these enzymes certainly contributes to the tissue injury characteristic of ALI/ARDS and appears to be a final step in a cascade of events triggered initially by TNF. For example, BAL fluid from patients at risk of ARDS contains increased amounts of TNF- $\alpha$ , IL-1, and IL-8. Specifically, elevated levels of IL-8 may be a positive predictive factor for the development of frank lung injury in patients at risk. Moreover, the BAL IL-8 level was associated with neutrophil concentrations correlated significantly with subsequent severity of lung injury and mortality. Finally, alveolar macrophages have been shown to actively produce chemotactic factors in patients with ARDS. Anti-(IL-4, IL-10, IL-13) inflammatory cytokines may play an important role alongside their better-characterized pro-inflammatory counterparts. A recent association between mortality rates and decreased concentrations of IL-10 and IL-1 receptor antagonist (rA) has been shown in patients with ARDS. It is therefore possible that ARDS represents the failure of anti-inflammatory cytokine responses in susceptible individuals as much as the activation of pro-inflammatory networks. Cytokines are also implicated in modulating events within the extracellular matrix, a dynamic network of lung parenchymal components crucial to the maintenance of normal alveolar architecture and permeability. Matrix metalloproteinases and the tissue inhibitor of metalloproteinase (TIMP) participate actively in the remodeling processes that follow lung injury. Their actions must be initiated by positive stimulation, including the release of inflammatory factors such as elastin. Survival of patients with ARDS clearly depends on effective alveolar repair, and in survivors the fibroproliferative response abates with the induction of programmed cell death (apoptosis). Understanding of the regulatory signals involved in the induction of myofibroblast apoptosis and the impact of positive pressure ventilation and other supportive interventions on these biologic processes are potentially of therapeutic significance. In particular, identifying the regulatory signals involving type II cell apoptosis and differentiation to a (normal) type I cell-dominated alveolar surface is a logical therapeutic direction to pursue.

Other potentially protective mechanisms that may soon be harnessed in patients at risk of developing ARDS/ALI involve

those relating to the heat shock response. This endogenous defense mechanism is widely conserved across species and cell lines. When triggered prior to an otherwise lethal injury, the heat shock response is protective in a variety of experimental systems. Thus, induction by brief hyperthermia or even by nonthermal means can protect rats against the lethal effects of experimental sepsis and other noxious stimuli. The time course and relative magnitude of the heat shock response after a stress condition varies widely among different cell types in the same organism. Until recently, much research pertaining to stress responses focused on issues relating to the regulation and mechanism of gene transcription. Only recently have the biologic changes coincident with the stress response, the properties of the individual stress proteins, and the protective effects that they engender been examined in detail. Stress responses triggered in experimental animals prior to the onset of injury can be protective and may attenuate the subsequent damaging effects of mechanical ventilation on the lung. Such results suggest that patients at risk for developing ARDS and sepsis might benefit from the use of a similar strategy.

#### Alveolar Capillary Membrane

A primary histopathologic characteristic of patients with ARDS is the development of noncardiogenic, high-permeability pulmonary edema. It was argued that measurements of vascular permeability should in theory be important to the diagnosis and evaluation of ALI/ARDS, although the practical difficulties associated with its measurement have hitherto prevented their widespread adoption. Thus, although chest radiography is the method most widely used to detect pulmonary edema, techniques for quantifying its accumulation in the lung have been less widely available. Indicator dilution methods have, however, been recently introduced in an attempt to measure extravascular lung water. Direct sampling and analysis of alveolar edema fluid for protein concentration have also been employed, as has the time-dependent accumulation in the interstitium of intravenously administered radiolabeled protein. Nevertheless, the development of alveolar edema has important consequences. First, there is an associated diminution in surfactant-associated phospholipid content, depending upon the severity of lung injury. Second, the relative quantities of the two most important phospholipids (phosphatidylcholine and phosphatidylglycerol) are markedly depressed. Third, an increase develops in a variety of lipids within surfactant, particularly phosphatidylethanolamine, phosphatidylcholine, inositol, and sphingomyelin. There is also preliminary evidence for an impressive decline in the content of surfactant-associated proteins. Plasma protein leakage inhibits surfactant function, which may increase surface tension, to cause alveolar instability with the development of atelectasis. Alterations in surfactant composition also may contribute to the disturbances of fluid balance seen in ARDS. Thus, increases in alveolar surface tension decrease interstitial and perivascular pressures and increase transendothelial fluid flux in the interseptal and interstitial spaces. Surfactant replacement therapy is therefore an attractive therapeutic possibility, although the results of initial studies have been disappointing. This may be due in part to inadequate delivery systems and the use of artificial as opposed to natural compounds in which the possible immunomodulatory capacity of surfactant-associated proteins are absent. Forthcoming studies will need to identify the optimum timing and dosage regimens for such interventions and critically address whether this approach represents merely an adjunct to ventilatory support or has an important impact

on inflammation, host defense, and mesenchymal proliferation in patients with established lung injury.

In the past 10 years the mechanisms that regulate the transport of fluid and protein across the normal alveolar epithelial barrier have been identified. Further, important new data have emerged regarding the mechanisms responsible for repair of the alveolar epithelial barrier in either hydrostatic or high-permeability pulmonary edema. In both circumstances there is a net influx of fluid from the vascular compartment to the interstitial space. The normal physiologic process of clearing alveolar fluid from the air spaces seems to require an active ion transport process. Active transport depends upon sodium uptake into channels on the apical membrane of alveolar type II cells, with subsequent extrusion to the basolateral interstitial space by the sodium-potassium ATPase pump. Chloride also moves from the alveolar to the interstitial space to maintain electrical neutrality by an incompletely identified pathway. Finally, water crosses the alveolar barrier to maintain iso-osmolar conditions, probably by a specific proteinaceous water transporter recently identified and described in the alveolar epithelium. Importantly, experimental studies suggest that basal alveolar fluid clearance can be accelerated by a variety of mechanisms. Specifically,  $\beta$ -adrenergic agonist therapy seems to increase alveolar liquid clearance in both animal and human lungs. There is also evidence to suggest that noncatecholamine-mediated mechanisms may be harnessed to achieve a similar end.

### Pulmonary Circulation

The endothelial damage that characterizes ARDS has profound implications for pulmonary vascular control. Impaired hypoxic pulmonary vasoconstriction is thought to account for most of the refractory hypoxemia that characterizes the condition. Changes in the molecular expression of mRNA coding for a variety of vasoactive mediators in pulmonary arteries taken from animal models of ARDS and in cultured and whole-vessel preparations of clinical specimens have been detected. Pharmacologic studies suggest that the inducible form of nitric oxide (NO) synthase modulates and attenuates an otherwise exaggerated hypoxic pressor response. The endogenous generation of NO appears to be attenuated in patients with ARDS to the extent that levels of exhaled NO are reduced in such circumstances. The increase in pulmonary vascular resistance that characterizes ARDS has profound implications for right ventricular function. Although right ventricular failure occurs rarely in these circumstances, it may be precipitated by the inappropriate application of certain modes of mechanical ventilatory support. Transthoracic and transesophageal echocardiography have identified impaired right (and sometimes left) ventricular function, particularly in patients with sepsis, shown to be improved by the use of inhaled vasodilators. The implications of right ventricular failure may be more profound in terms of back pressure acting upon the systemic venous and splanchnic circulations. In particular, increased small-bowel mucosal permeability consequent to venous congestion may be responsible for the translocation of endotoxin and bacteria, contributing to the high incidence of nosocomial pneumonia identified in these patients. Lastly, it would be naïve to consider that endothelial abnormalities and changes in vascular control are confined to the pulmonary circulation. It is becoming clear that ARDS in many senses represents only the pulmonary manifestation of a panendothelial response. Abnormalities of peripheral oxygen uptake and utilization may be responsible for a loss of microvascular control or, alternatively, for direct toxic effects on mitochondrial utilization of oxygen.

### MECHANICAL VENTILATORY SUPPORT

The therapeutic interventions currently available or now at the fringes of clinical practice were discussed. Our understanding of the mechanics of the diseased respiratory system is still evolving. It is increasingly recognized that chest wall mechanics play an important role in distributing ventilation and perfusion by influencing the pressure-volume characteristics of the integrated respiratory system. The strong implication for clinical practice is that the pressure-volume relationship measured routinely at the bedside must be interpreted very carefully when it is used to select the ventilatory pattern and settings for positive end-expiratory pressure (PEEP). Moreover, modification of chest wall mechanics (for example, by prone positioning) can be exploited to improve ventilation-perfusion matching and perhaps minimize ventilator-induced lung trauma.

Strong laboratory evidence and emerging clinical data reinforce the need to prevent persistent or tidal re-expansion or collapse of inflamed tissue. The mechanics of recruitment were reviewed, with specific references to the regionality of collapse, the time dependence of the recruitment process, recruiting maneuvers, variations of body position, and the interactions between tidal volume and PEEP in establishing and maintaining alveolar patency. Despite the value of the inspiratory pressure-volume curve, it is increasingly clear that there also is a need to focus on the expiratory limb of this relationship and to develop clinical techniques to identify the optimal combination of PEEP and tidal volume. Thus, although high tidal volumes can themselves incite damage, optimal recruitment may require periodic applications of sustained high airway pressure ("recruiting maneuvers"). The importance of these concepts was brought into clinical perspective by reviews of data from prospective, randomized, controlled trials of ventilation strategies. A clinical approach designed to maximize lung recruitment by limiting peak tidal alveolar pressure and adjusting PEEP according to the inspiratory pressure-volume characteristics of the respiratory system succeeded in improving mechanics, gas exchange, hemodynamics, and mortality in comparison to a conventional "least acceptable PEEP" guideline. Intriguingly, a majority of the mortality benefit difference emerged within the first 72 h of treatment—the precise interval over which mortality has not been shown to fall convincingly over the past two decades, during which conventional ventilator treatment has prevailed. A well-designed and executed trial involving 25 centers in Europe and North America targeted tidal volume to be the main independent variable, whereas end-expiratory pressure did not differ between groups. The mean plateau pressure was less than 33 cm H<sub>2</sub>O in both. In this specific context of identical PEEP and moderate plateau pressures, no mortality difference was observed despite significantly different tidal volumes.

Although patients with ARDS do not usually present major difficulties in ventilator withdrawal once oxygenation improves, problems occasionally arise, in part because they have an increased ventilatory burden and are predisposed to muscle weakness by the use of sedatives, paralytics, and corticosteroids. The importance of a brief trial of spontaneous breathing in speeding ventilator disconnection was stressed.

### NONVENTILATORY SUPPORT

The current status of extracorporeal membrane oxygenation (ECMO) and CO<sub>2</sub>(ECCO<sub>2</sub>R) removal in the management of ARDS has been influenced by recent advances in surgical technique and anticoagulation, which have enabled patients treated by experienced medical teams to continue extracorp-

real support for weeks, with eventual successful discontinuation. However, the methodology remains extremely resource-intensive and beset by complications. The most devastating of these has been intracranial hemorrhage, a complication seen more frequently in patients managed prior to  $\text{ECCO}_2\text{R}$  with permissive hypercapnia. It was urged that the technique not be abandoned but rather applied selectively by experienced, well-supported centers to those patients with disease refractory to other therapies.

Simpler measures, such as prone positioning, have been demonstrated to improve oxygenation in many patients with ARDS. Laboratory-based experimental data confirm that prone positioning beneficially redistributes end-expiratory lung volume toward dorsal regions, which remain well perfused. The mechanics governing the response of human patients to prone repositioning are complex. Although 70% of patients with ARDS respond at least temporarily to prone repositioning, 30% do not. This differential response may relate in part to disease type and stage, as well as variations in chest wall contour and compliance. Interestingly,  $\text{PaO}_2$  appears to improve most when chest wall compliance declines significantly in the transition. Such data suggest that the intrapulmonary redistribution of lung volume and ventilation are instrumental in determining the value of this technique for improving oxygen exchange.

The pharmacologic manipulation of ventilation and perfusion in acute lung injury has been dominated in recent years by the use of inhaled nitric oxide (NO). The majority of the potential response to NO with respect to gas exchange is achieved with an inhaled concentration often less than 10 parts per million, whereas the response to pulmonary hypertension continues into a higher dosage range. Inhaled prostacyclin vasodilates as effectively as NO, but does not confer as much oxygenation benefit. Because inhaled NO is more efficient when the lung is recruited, provision of sufficient PEEP is important in optimizing its benefit. Further, NO has possible antioxidant as well as oxidant properties, although it has not been shown to reduce mortality in controlled trials. Electrochemical (as opposed to chemiluminescence) monitoring is generally sufficient for clinical purposes, and scavenging exhaled gas is not generally necessary because of the low concentrations of NO in the expired airstream. Five parts per million may be the optimal dosage based on the experience of a recently completed multicenter randomized trial of inhaled NO in ARDS conducted in the United States. The simultaneous systemic delivery of an intensifier of hypoxic pulmonary vasoconstriction (almitrine bismesylate) magnifies the effectiveness of inhaled NO on gas exchange. Interestingly, patients with pneumonia showed better responses to this combined treatment than did those patients with ARDS.

### PARTIAL LIQUID VENTILATION

Liquid ventilation with perfluorocarbons is at the very frontier of current clinical practice. The physiology of liquid breathing with regard to gas exchange and mechanics was reviewed. Potentially, perfluorocarbon-aided gas exchange may have multiple therapeutic benefits for patients with ALI/ARDS. Existing laboratory evidence indicates protective effects of perfluorocarbons against lung injury and infection. Apart from acting as a barrier to infection, perfluorocarbon instillation may reduce surface tension, re-distend collapsed alveoli, or cleanse them of inflammatory debris. Although its clinical value is hardly proven, initial experience in the pediatric setting has been promising.

A recently completed FDA-required phase II ("proof of principle") trial of partial liquid ventilation has indicated a tendency for younger patients to require fewer days of ventilator support and reduced mortality, although basic questions must be answered before perfluorocarbon-aided gas exchange can be advocated for widespread clinical use.

### CONDUCT OF FUTURE CLINICAL TRIALS IN ARDS

The conduct of clinical trials has assumed increasing importance over the past decade in the attempt to identify cost-effective treatments. It is essential that cooperative efforts be carried out to elucidate rather than obscure the questions of interest. Because many aspects of practice may indirectly influence the outcome variable, there is a need for co-intervention control to maximize the signal-to-noise ratio, both in single and multicenter clinical studies. Impediments to accurate judgment are imposed by incorrect correlations, preconceived notions, lack of awareness, overconfidence, and hindsight bias. Tighter control of co-interventions by protocol is needed to amplify the power of these studies. The characteristics of an ideal clinical trial were reviewed, and the importance of precise definitions, appropriate timing, and prudent selection of dose and duration of the intervention(s) was emphasized. The questions selected must be mature and scientifically well researched, with testable hypotheses and appropriate endpoints. There is also a need to ensure that the interventions proceed as intended during the conduct of the trial. Mandates to separate clinical caregivers and research personnel, data collectors and data managers, sponsors and investigators, and safety board and study personnel characterize the well-planned and executed clinical trial.

Prospects for future multicenter trials of ventilatory support were considered. Cooperative networks have developed both in Europe and in North America via which appropriate questions can be tested in adequate numbers of patients by experienced investigators. The approach taken in the ongoing National Institutes of Health-sponsored trial of "high stretch" tidal volumes in the treatment of ARDS was reviewed, thereby illustrating how an appropriate algorithm can be used for co-intervention control of clinical practice variations. Exciting possibilities exist for the use of well-tuned cooperative networks to study pharmacologic interventions aimed at interrupting key points in the inflammatory process. To date, most clinical trials have been fruitless, but better understanding of the complex interactions among cellular, extracellular, and intracellular messengers and mediators are cause for guarded optimism. The pressing need to establish valid biomarkers of patients at risk to improve drug targeting was emphasized.

### SUMMARY

The Round Table on Acute Lung Injury proved a stimulating forum for the interchange of ideas regarding the state of the field and afforded many opportunities for scientific interaction-both during and outside the formal program. The participants are indebted to the European Society of Intensive Care Medicine and to the American Thoracic Society for their sponsorship, as well as to the local organizing committee and secretariat for coordinating a professionally valuable and memorable educational event.

### References

1. Marini, J. J., and T. W. Evans, editors. 1998. *Acute Lung Injury*. Springer-Verlag, New York. 1-458.

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