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The American-European Consensus Conference on ARDS, Part 2

Ventilatory, Pharmacologic, Supportive Therapy, Study Design Strategies and Issues Related to Recovery and Remodeling

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Abstract The acute respiratory distress syndrome (ARDS) continues as a contributor to the morbidity and mortality of patients in intensive care units throughout the world, imparting tremendous human and financial costs. During the last ten years there has been a decline in ARDS mortality without a clear explanation. The American-European Consensus Committee on ARDS was formed to re-evaluate the standards for the ICU care of patients with acute lung injury (ALI), with regard to ventilatory strategies, the more promising pharmacologic agents, and the definition and quan-

tification of pathological features of ALI that require resolution. It was felt that the definition of strategies for the clinical design and coordination of studies between centers and continents was becoming increasingly important to facilitate the study of various new therapies for ARDS.

Key words Adult respiratory distress syndrome · Acute lung injury · Mechanical ventilation · Pharmacologic therapy · Lung remodeling · Supportive care · Coordination

Introduction

Despite advances in supportive care, the mortality rate in patients with the acute respiratory distress syndrome (ARDS) is widely considered to have remained high, and generally in excess of 50% [1]. Recent data suggest a significant decrease in fatality rates for ARDS, though the explanations for this observation are not clear [2]. Large multicenter prospective controlled randomized trials are needed to provide definitive answers concerning the efficacy of new and existing therapies. These trials generally must address two considerations: first, basic research which links the proposed new treatment to important pathophysiological components of ARDS; second, the risk-benefit ratio of the treatment to be tested [3]. It may be naive to assume that any single therapy will be a "magic" bullet to treat all aspects of ARDS.

Under the auspices of the American Thoracic Society and the European Society of Intensive Care Medicine, a series of meetings were held in conjunction with

the American Thoracic Society Annual Meeting on May 15, 1993 in San Francisco, California; May 22, 1994 in Boston, Massachusetts; the European Society of Intensive Care Medicine Annual Meeting on October 26, 1992 in Barcelona, Spain; June 17, 1994 in Innsbruck, Austria; and on September 27, 1996 in Glasgow, UK. This second American European Consensus Conference on ARDS [4] was organized in an attempt to analyze the pathophysiologic mechanisms of lung damage as they relate to mechanical ventilation strategies and to promising agents which may ultimately be shown to have utility in the treatment or prevention of ALI and ARDS. In addition, the increasing costs of care associated with only marginally perceived additional benefits of novel therapies prompted the Consensus Committee to re-evaluate the current treatment of ALI/ARDS. In order to analyze the recovery from ALI, an attempt was made to define the clinical and pathological features of ALI that require resolution and how these should be defined and quantified.

The members of the Consensus Committee were divided into subcommittees, each of which was charged with discussing and developing a position paper on at least one aspect of the problem. These position papers were presented to the entire Committee for comments and discussion. When the Committee reached agreement, specific modifications were made to the position papers. The following subcommittee reports are a result of this consensus process.

Subcommittee I: ventilatory strategies for ARDS

Background

Although ARDS has previously been considered a problem of *diffuse* lung injury and a generalized increase of tissue recoil, it now appears that the radiographic, densitometric, and mechanical consequences of ARDS are heterogeneous [5]. In severe cases, the inflation capacity of the lungs may be less than one-third of normal. The compliance and fragility of tissues comprising the aerated compartment in ARDS are likely to be more functionally normal than previously envisioned, especially in the earliest phase of this disease [5,6]. Computed values for airway and tissue resistance are elevated in ARDS [7], an observation that is perhaps best explained by the reduced number of patent airways. The refractory hypoxemia of ALI can be enhanced by supplementing inspired O_2 and by raising mean and end-expiratory alveolar pressures. Each of these interventions, however, has associated risks and benefits. Animal studies have shown that high fractions of inspired O_2 and high cycling pressures are potentially injurious, [8,9–19], especially when applied over extended periods [20], superimposed on pre-existing damage [12], or combined with other injurious agents [21].

Widely held objectives of ventilation in the setting of ALI have given priority to “normalizing” arterial blood gases and avoiding depression of cardiac output. Until recently respiratory system pressures in humans have been monitored but not tightly constrained [6,22]. Flow controlled, volume cycled ventilation, using tidal volumes of 10–15 ml/kg has previously been the standard of practice in the management of ARDS and most other problems of adult ventilatory support. Mean airway pressure, as a clinically measurable reflection of mean alveolar pressure, relates fundamentally to oxygen exchange, cardiovascular performance, and fluid retention *under conditions of passive inflation* [23]. Positive end-expiratory pressure (PEEP) has been used to increase end-expiratory trans-alveolar pressure and volume, and thereby to improve gas exchange. The alveolar pressure that determines aerated volume at end-expiration is the sum of deliberately applied PEEP and that which may arise by dynamic hyperinflation (auto or intrinsic

PEEP). The latter may often be significant in ALI/ARDS due to high minute ventilation, the use of extended inspiratory time fractions, and the elevated resistance of the native airway, endotracheal tube and exhalation valve.

All forms of barotrauma described in the pediatric literature, including interstitial emphysema, tension cysts, systemic gas embolism, and damage similar to bronchopulmonary dysplasia, have now been recognized in patients with ARDS [24]. In experimental animals, the choice of ventilatory pattern influences the morphology of normal [15,19,20] and previously injured tissue [12]. From these animal studies it is suspected that excessive *regional* volumes are damaging, whether produced by positive or negative pressure.

Ventilatory patterns that apply high transalveolar stretching forces cause or extend tissue edema and damage in experimental animals [8,10,11,13,15,18]. Recent work strongly suggests that regional overdistention is commonly produced in patients with ARDS by static airway pressures > 30 cm H_2O [25], a pressure level known to cause damage in sheep when sustained for more than a few hours [20]. Although excessive tidal volume must be avoided, animal studies suggest that periodic inflations with a relatively large and sustained volume may be needed to avoid collapse of unstable lung units when very small tidal volumes (< 4 – 5 ml/kg) are used [26]. Judging from the substantial delay to peak incidence of pneumothorax, the lung appears to be able to withstand exposure to somewhat higher forces in the earliest phase of human ARDS without *radiographically evident* barotrauma [16,17]. Later in the course of illness the strong collagen infrastructure of the lung degrades unevenly, so that similar pressures are more likely to result in overt alveolar disruption (e.g., pneumothorax, pneumomediastinum, gas cyst formation).

Animal studies indicate failure to preserve a certain minimum end-expiratory transalveolar pressure in the early phase of ARDS may intensify pre-existing alveolar damage, especially when high tidal volumes are used [10,13,15,19,27]. Indeed, the shear forces associated with tidal collapse and reinflation of injured alveolar tissues may be responsible for an important component of ventilator-induced lung damage. The end-expiratory pressure required to avert widespread alveolar collapse varies with the hydrostatic forces applied to the lung. Consequently, a higher pressure is required in patients to prevent atelectasis in dependent regions than in the regions more superior [5,28]. Gravitational factors, therefore, help to explain the strikingly dependent distribution of radiographic infiltrates shortly following the onset of lung injury, as well as reversal of these infiltrates and improved arterial oxygenation in the prone position [29–32]. In experimental animal studies, total PEEP sufficient to place the tidal volume above the ini-

tial low compliance region of the static pressure-volume relationship of the respiratory system (Pflex) appears to attenuate the severe hemorrhagic edema otherwise induced by high ventilating pressures [10,14,15].

Stress failure of the pulmonary capillaries with resulting extravasation of formed blood elements may occur at trans-vascular pressures that exceed 40–90 mmHg, depending on animal species [33,34]. Although the relationship of this observation to the hemorrhagic edema of experimental (ventilator-induced) lung injury remains unclear, trans-capillary mechanical forces of comparable magnitude may be generated in ARDS when high tidal volumes and peak static tidal pressures are used. High vascular pressures and blood flows may also be important determinants of lung injury.

Certain adjuncts to conventional ventilation, such as nitric oxide inhalation [35], tracheal gas insufflation [36,37] and perfluorocarbon associated (partial liquid) ventilation [38–41] currently show promise to improve transpulmonary gas exchange; other approaches, such as surfactant administration [42] and inhaled prostacyclin [43], may eventually prove beneficial.

Controversies

Detailed clinical information is not available for guidance regarding the maximally safe peak and mean alveolar pressures that can be applied for extended periods without inducing alveolar damage or retarding healing. Although failure to preserve a certain minimum end-expiratory transalveolar pressure has been shown experimentally to intensify pre-existing alveolar damage [10,27], this phenomenon has not yet been clearly demonstrated in humans. Consequently, expert opinion differs on whether applying the least PEEP that accomplishes adequate gas exchange or the guarantee of some minimal value of end-expiratory alveolar pressure is the best course to follow within the first few days of the disease process [6,44–46]. Periodic application of sustained high inflating pressures so as to recruit unstable lung units continues to be advocated by some highly knowledgeable investigators, especially when small tidal volumes are used, as in high frequency ventilation [26]. The appropriate tidal volume to use undoubtedly varies with the level of PEEP [13,47]. There is no consensus regarding the contribution of vascular pressures, position changes, infection, inspired oxygen concentration and other clinical variables on the incidence and intensity of ventilator induced lung injury.

Among the most pressing questions related to the ventilatory management of ALI are those which concern the development of guidelines for setting appropriate targets for alveolar ventilation and oxygenation. Allowing PaCO₂ to rise to supernormal values (permissive hypercapnia) appears to be an effective strategy for lim-

iting the need for ventilatory pressure [22,48,49]. The full effects of hypercapnia on such important variables as gas exchange, cardiovascular dynamics, and tissue edema have yet to be determined in this setting [48,49]. Elevated FIO₂ and high ventilatory pressures are often required to achieve near complete saturation of arterial blood with oxygen. The conditions (if any) under which arterial O₂ saturation can be allowed to fall to subnormal values without unacceptable clinical consequences have not yet been delineated. There is no clear consensus regarding the most appropriate indicator of regional or global adequacy/inadequacy of O₂ delivery (dysoxia) for routine clinical use.

The combinations of O₂ concentration and exposure duration which produce significant lung damage have not been firmly established in the setting of ARDS, and may well vary with disease severity and individual susceptibility. Similarly, although a considerable body of experimental data has been accumulated, detailed information is not yet available regarding which ventilation pressures and patterns of ventilation are safe to apply for extended periods. In the absence of definitive data obtained in a clinical context, some knowledgeable practitioners increase lung volume in an attempt to minimize FIO₂, whereas others prefer to use higher inspired fractions of O₂ rather than increase peak, mean, and end-expiratory airway pressures. Although absolute agreement was not reached, the majority of the consensus conferences believe that limiting airway pressure takes precedence over limiting FIO₂. A very recent prospective randomized study from a single institution indicates improved lung mechanics, gas exchange, and respiratory mortality by following a strategy emphasizing ventilation with reduced alveolar pressure and tidal volume [50]. Yet, one well conducted prospective comparison of a modern approach that included inverse ratio ventilation and extrapulmonary CO₂ removal (when necessary) to a more conventional strategy was unable to detect a significant outcome difference between them [51].

Most clinicians recognize the need to control maximum alveolar pressure and are cognizant of a connection between mean alveolar pressure and arterial O₂ tension; however, there is no uniformity of opinion regarding the best mode and method of ventilatory support. Specifically, whether different methods for achieving a similar mean airway pressure (such as high level PEEP) and inverse ratio ventilation [52] differ with respect to risks and benefits has not been adequately examined. The extent to which spontaneous (versus controlled) ventilation should be encouraged has also been an area of uncertainty. There is renewed interest in high frequency ventilation applied at an appropriate mean lung volume as a ventilatory strategy for ARDS [53], but the basis of this enthusiasm remains primarily theoretical and experimental at this time.

Several recent studies have addressed the topic of risk and benefit for manipulation of oxygen delivery [54–56]. Because mechanical ventilation can benefit or impair O₂ delivery, such observations may hold implications for its implementation. These are discussed in more detail in the section on General Supportive Care.

Recommendations

1. Goals of ventilatory management: Ensure appropriate O₂ delivery to vital organs along with sufficient CO₂ removal to maintain homeostasis, to relieve an intolerable breathing workload, and to avoid either extending lung damage or preventing tissue healing.
2. Minimize Oxygen Toxicity: A high fraction of inspired oxygen by mask may be used for brief periods as a temporizing measure. Most investigators, however, take aggressive steps to reduce the fraction of inspired oxygen (e.g., increase mean airway pressure, improve cardiovascular function, undertake diuresis, or accept somewhat lower values for O₂ saturation) whenever FIO₂ exceeds 0.65.
3. Recruit Alveoli: At a given level of minute ventilation, mean airway pressure can be increased by adding PEEP or by extending the inspiratory time fraction. Although recruitment of alveoli may continue throughout much of the tidal range, total PEEP values that obliterate the lower inflection zone (P_{flex}) of the inspiratory static pressure-volume curve of the respiratory system (total PEEP of 10–15 cm H₂O in most instances) attempt to ensure nearly complete recruitment. Whether further increments of mean alveolar pressure are best made by adding more PEEP or by extending the inspiratory time fraction is debated. The least mean airway pressure should be used that accomplishes acceptable arterial oxygenation at a nontoxic concentration of inspired oxygen. The full impact of changes in PEEP on gas exchange and respiratory system compliance may not be fully developed for hours.
4. Minimize High Airway Pressures: Strategies that reduce the exposure of the lung to high pressures include permissive hypercapnia, pressure controlled ventilation, and pressure limited, volume cycled ventilation. Based on the available experimental literature, maximal *transalveolar* pressure should not exceed 25–30 cm H₂O during each tidal cycle. This usually corresponds to 30–40 cm H₂O end-inspiratory static (plateau) pressure, depending on lung and chest wall compliance. [25].
5. Prevent Atelectasis: It may be advisable to periodically use larger volume, higher pressure breaths of longer inspiratory duration to forestall atelectasis when very small tidal volumes and/or low PEEP values are used.
6. Use Sedation and Paralysis Judiciously: In seriously affected patients, deep sedation (occasionally supplemented by nondepolarizing muscle relaxants) may be

needed whenever VO₂ demands must be minimized to address hypoxemia or reduced cardiovascular reserve, or when an uncomfortable or poorly tolerated ventilatory pattern, such as inverse ratio ventilation is selected. Any use of pharmaco-paralytic agents should be brief with frequent reassessment of depth and continued need.

Future research questions

1. What is the contribution of each of the following to the development of ALI? Does it vary with the nature of the underlying pathological process? Do each of the following contribute equally to tissue injury?
 - a. Peak alveolar pressure
 - b. Peak *transalveolar* pressure (regional volume)
 - c. Peak airway pressure
 - d. Shearing stresses
 - e. Mean alveolar pressure
 - f. Inadequate end expiratory lung volume
2. What are the interactions among the above that contribute to ventilator-induced lung injury and do these vary with the nature of the underlying process?
3. What is the safe upper limit for transalveolar pressure? Is barotraumatic tissue injury time- or frequency dependent? Does it vary with the nature or phase of the tissue injury process? Should the ventilatory strategy be altered accordingly?
4. What impact do less conventional ventilatory strategies and therapeutic adjuncts such as permissive hypercapnia, inverse ratio ventilation, airway pressure release, ECCO₂R, proportional assist ventilation, partial liquid ventilation, prone re-positioning, nitric oxide inhalation and extrapulmonary intracaval gas exchange have on the generation of barotrauma, the extension of tissue injury, and the gas exchanging functions of the lung?
5. What are the relative contributions of increased FiO₂ and airway pressure to the development of lung injury?

Clinical strategies for ventilatory support

6. Is ventilator-induced lung injury related to local or systemic infection, or to the generation of multisystem organ failure?
7. Under which condition(s) is a subnormal PaO₂ tolerable? How is adequacy of tissue O₂ delivery best assessed? What are the acceptable limits for pH, PaCO₂ and PaO₂?
8. How can overdistention (*regional* tissue volumes) best be monitored in the clinical setting?

9. How are the respiratory muscles and ventilatory control affected in ARDS? Are normal strength and endurance preserved? What are the relative merits and disadvantages of modes that encourage spontaneous breathing effort?

10. Does the choice of breathing pattern or contour of gas delivery influence ventilation-perfusion matching, arterial oxygenation, and/or the impedance to pulmonary blood flow?

11. What are the merits of adjunctive measures, such as prone positioning, partial liquid ventilation, extrapulmonary gas exchange, and tracheal gas insufflation?

Subcommittee II: pharmacologic treatment

Background

Substantial advances have been made in the understanding of the pathogenesis of ARDS and ALI using *in vitro* systems, animal models, and clinical studies [57–62]. Although no single clinical feature or measurable marker has been indentified that clearly predicts which patients will develop the syndrome, numerous circulating mediators and inflammatory cell functions have been studied. It has been well documented that carefully defined at-risk groups (i.e., patients with sepsis syndrome) are associated with a predictable incidence of ARDS [63]. Numerous circulating inflammatory mediators including complement fragments, endotoxin, thromboxane, leukotrienes, proteases, cytokines and platelet activating factor (PAF), to name a few, are variably present in both patients at risk for, as well as those with ARDS, and may contribute to the development of the syndrome [64,65]. Studies of circulating inflammatory cells suggest that not only are there differences between major cell categories (i.e., lymphocytes and neutrophils) in response to systemic inflammation, there are sub-populations of these cells with vitally different roles [57,59]. Recent work has shown that at the same time hydrogen peroxide (H_2O_2), serum catalase, manganese-superoxide dismutase (MnSOD) and ceruloplasmin are increased, glutathione is decreased. Findings such as these suggest that the balance between oxidants and anti-oxidant capacity may be important [57,58,66,67]. Clearly proteases are released into the lung and the circulation during acute systemic inflammation.

Although no single biochemical marker specifically predicts the development of ALI or multiple organ dysfunction syndrome (MODS), persistent neutrophilia, increased proteases, IL-8, TNF- α , arachidonic acid metabolite levels, and decreased glutathione in the bronchoalveolar lavage fluid may be associated with an increased mortality [65–69,70, 71, 72]. Most studies to date have focused on a single marker, cell response or

lavage feature. Clearly, the complexity of ARDS suggests studies be broad to evaluate multiple markers together.

Apart from the standard measures of mechanical ventilation, fluid management, etc., there are potentially other means to support the failing lung being explored experimentally. Nitric oxide therapy and surfactant replacement may be thought of in this category since there is no clear evidence that either will correct the underlying tissue damage but each may substantially improve patient management [35,42,73,74]. Nitric oxide, a gas with potent pulmonary vasodilating properties, lends itself well to this route since it is desirable for this agent to be delivered only to the ventilated areas of lung. Since surfactant function is clearly impaired in patients with ARDS, it is attractive to consider replacement of surfactant as a therapeutic option. A unique aspect of the lung is that therapy delivered by inhalation is feasible under certain conditions [42,75]. However, caution is advised regarding certain technical limitations of this approach [76,77]. The tendency of surfactant to spread easily throughout the lung allows consideration of airway administration even in patients with severe lung pathology. This is also true for nitric oxide. Other creative pharmacological interventions that may be supportive of optimal ventilation-perfusion matching have been proposed (see below).

Finally, a variety of growth factors for lung repair such as vitamin A, necessary for re-epithelialization as well as other processes of repair, may be extremely important in ALI/ARDS [78–81]. These kinds of interventions take on added significance when one considers the fact that the time window between the recognition of a patient at risk for ALI and the development of ALI may be small to non-existent. This may, in fact, be true for most patients with ALI/ARDS. Thus, enhancement of the repair process would possibly be the best approach to such patients.

Controversies

A confounding factor in the clinical application of inhibitors of the inflammatory response is the potential importance of tolerance to mediator/neutrophil-induced injury. Efforts to evaluate the role of neutrophil heterogeneity in ARDS and to better define the role of mediators, inflammatory cells, gene expression, physiologic responses, lung repair and multiple organ dysfunction syndrome in critically ill patients will need to be conducted in parallel with evaluations of new therapeutic agents [59,78–80, 82].

The mechanisms presumed responsible for the pathogenesis of ARDS have been reviewed here and elsewhere [83,84]. The most commonly accepted model is that a wide variety of initiating stimuli trigger an in-

flammatory cascade in which cells release mediators which can either further amplify the cascade, directly harm the lungs, or both. These mediators include eicosanoids, platelet activating-factor, cytokines, proteolytic enzymes, oxygen radicals, thrombin, activated complement and others. The result of this process is increased endothelial and epithelial permeability, increased pulmonary vascular pressures, altered lung mechanics, and impaired alveolar surfactant function. Further, there is substantial animal data suggesting that accentuation of the pulmonary injury may occur with modes of ventilation which result in over-distention of the lung [19].

The promulgation of an ever increasing variety of agents designed to reduce inflammation has caused concern that interference with the immune system in these ways may produce a bad outcome, especially with regard to infection control. This fear has not been realized in any published study to date, including the studies of high dose methylprednisolone. Conversely, it has been proposed that immune stimulation may be an appropriate consideration for clinical prevention or management.

Investigations

Proposed ARDS pharmaco-therapies can be placed in one or more of the following categories:

Anti-endotoxin immunotherapy: Though there are a variety of potential approaches to endotoxin antagonism, only monoclonal antibodies have received extensive human investigation. Several large clinical trials using these monoclonals have been conducted showing little or no survival benefit to patients with sepsis syndrome [85,86]. However, recent significant advances in the understanding of the mechanisms by which endotoxin interacts with cells has provided many new targets. Lipid x (a derivative of endotoxin), bacterial permeability increasing protein (BPI), and polyclonal antibodies (sheep derived), all offer the possibility of endotoxin neutralization rather than simply binding. None of these latter agents have reached large scale clinical testing.

Corticosteroids: There now appears to be general agreement that corticosteroids are not useful in the acute management of sepsis and ARDS. No overall change in the mortality of sepsis has been demonstrated, and corticosteroids do not seem to reduce the incidence of ARDS secondary to sepsis [87]. Further, steroids do not seem to improve either physiologic parameters or mortality early in the course of established ARDS of various etiologies [88]. Corticosteroids may be of value in ARDS variants, such as the fat embolism syndrome, and pneumocystis carinii pneumonia, where corticosteroids may be of value as a prophylaxis or therapy

[89–92]. Steroids have also been suggested as potential treatment for the later, “fibroproliferative” phases of the disorder by several anecdotal reports [93]. There has been only one prospective randomized trial, a pilot study of 24 patients, which suggests this therapy may be beneficial [94].

Cyclooxygenase inhibitors: Cyclooxygenase metabolites of arachidonic acid appear to be integral to the pathogenesis of sepsis-related ARDS. Of primary interest are thromboxane A₂ (TxA₂), a vasoconstrictor and promoter of platelet aggregation; prostacyclin (PGI₂), a vasodilator and inhibitor of platelet aggregation; and prostaglandin E₂ (PGE₂), a vasodilator with immunosuppressive effects and leukotrienes. Studies of ibuprofen in sepsis patients showed reduction in the levels of these mediators and that there may be important physiologic clinical benefits of such treatment [95, 96]. Antagonism of thromboxane alone with ketoconazol has also been explored clinically with encouraging results [97].

Antagonism of pro-inflammatory cytokines: The cytokines of particular current interest in sepsis and ARDS are tumor necrosis factor alpha (TNF- α), interleukin-1b (IL-1), interleukin-6 (IL-6) and interleukin 8 (IL-8). Normally present in small quantities, these compounds are thought to have important roles in host defense. TNF has effects which, to a large extent, resemble those of endotoxin. Exogenous TNF infusion leads to a sepsis-like syndrome with ARDS-like lung injury and death in animal models. Circulating levels of TNF rise in human sepsis and correlate with mortality and antibodies to TNF- α may reduce mortality in some subsets of septic patients, though ARDS and ALI have not been specifically studied [60,98–99]. Studies attempting to antagonize the effect of IL-1 have failed to demonstrate clinical benefit [100].

Platelet-activating factor inhibitors and receptor antagonists: Platelet activating-factor (PAF), a lipid mediator derived from the membrane phospholipids of a variety of cells, is an extremely potent inflammatory mediator. PAF promotes platelet aggregation, activates granulocytes, alters vascular tone, and increases vascular permeability and airway responsiveness. There are no data to date which suggest PAF antagonist will be useful in ARDS [61,101].

Pentoxifylline: Pentoxifylline is a xanthine derivative currently in use for its ability to improve perfusion in human peripheral vascular disease, but is also known to inhibit oxygen radical release, platelet aggregation, phagocytosis, and responsiveness to PAF. It also inhibits the release of TNF into the circulation of mice, rats, and humans in response to intravenous exposure to endotoxin and appears to block the physiologic responses to

endotoxin. These data suggest that pentoxifylline may be of value in human sepsis and ARDS, but randomized trials need to be performed [102, 103]. A related compound, lisophylline, is currently in Phase II/III clinical trials.

Lipid mediators (prostaglandins E_1 and E_2): ARDS is associated with changes in pulmonary hemodynamics which probably results from active vasoconstriction and the loss of microvasculature. Thus, vasodilator therapy has theoretical appeal. Prostaglandin E_1 (PGE_1) is a vasodilatory lipid mediator which in various models reduces pulmonary artery pressure and the rate of lung extravascular fluid accumulation, improves gas exchange and attenuates release of leukotriene B_4 , oxygen radicals, and cytotoxic enzymes from activated granulocytes [104]. A prospective trial in surgical patients demonstrated a significant survival benefit at 30 days, but a subsequent prospective multi-center trial in medical and surgical ARDS patients did not show increased survival [105,106]. Another multi-center trial is currently in progress in which liposome encapsulated PGE_1 will be used. Anecdotal information suggest that aerosol as well as liposomal PGE_1 may accomplish some of the goals of therapy on lung function without causing systemic hypotension.

Antioxidants: Highly reactive free radical metabolites of oxygen, including hydrogen peroxide (H_2O_2) and the hydroxyl radical (OH), are released by activated inflammatory phagocytes. They are normally held in check in the lung by elaborate defense mechanisms which include antioxidant enzyme systems (e.g., superoxide dismutase [SOD], catalase, and the glutathione [GSH] redox cycle) and various small-molecular-weight soluble oxidant scavengers (e.g., vitamin E, beta-carotene, vitamin C and uric acid) [58, 67, 107–109]. It has been proposed that in ARDS these defenses may fail and expose lung and other tissues to oxidant damage. Pharmacological strategies to enhance pulmonary antioxidant defenses include augmentation of stores of antioxidant enzymes (superoxide dismutase, catalase), augmentation of glutathione stores (N-acetylcysteine, oxothiazolidine carboxylate, glutathione), and addition of small-molecular-weight free radical scavengers (vitamin E). [67,109–113,114]. A Phase III clinical trial of oxothiazolidine carboxylate is currently underway.

Antiproteases: Enzymes such as the serine proteases, elastase, collagenase, and gelatinase may be important products of phagocytic inflammatory cells and may be involved in ARDS [59]. A majority of ARDS patients have elevated levels of proteolytic enzymes in various states of activity in bronchoalveolar lavage (BAL) fluid in the form of neutrophil elastase and collagenase

[57,59,68,69,115]. Collagenase is present in the plasma of septic patients and normal volunteers given endotoxin but not in normal plasma (unpublished data). There are animal data that suggest that exogenous antiproteases can block lung injury [59].

Inhaled pulmonary vasodilators (nitric oxide, PGE_1 , PGI_2): Pulmonary hypertension seen in ARDS may contribute to the degree of pulmonary edema and circulatory dysfunction. These alterations may adversely affect patients with ARDS because the increase in PVR may: 1) produce excessive strain on the right ventricle and cause a decrease in cardiac output or right ventricular failure; 2) adversely affect patients with multiple systems organ failure or ARDS by interference with ventilation perfusion matching; 3) transmit high pulmonary artery pressures to the microvasculature contributing to protein leak and pulmonary edema [73]. In many cases, chest radiography fails to demonstrate pulmonary edema, yet patients are severely hypoxemic. This condition is sometimes referred to as the non-edematous ARDS (NARDS) [116]. It seems likely that this process is driven by the net effect of a combination of opposing factors including endogenous vasodilators and broncho-constrictors producing severe ventilation-perfusion mismatching. In ARDS, where large areas of the alveolar bed are flooded, it is likely that loss of these important homeostatic mechanisms can result in severe, refractory hypoxemia. Inhaled nitric oxide produces microvascular dilation in those areas accessible to the gas. There are published data indicating that nitric oxide reduces pulmonary artery pressure and shunt, and increases PaO_2/FIO_2 ratio while not effecting cardiac output or systemic arterial pressure [35,73,74]. However, a recent randomized trial of 177 patients using 4 doses of nitric oxide (range 1.25–40 parts per million) failed to show improvement in survival or duration of mechanical ventilation. There was a trend toward better outcome in the group receiving 5 parts per million. (presented by P. Dellinger, Mar., 1997, Brussels, Belgium.) Anecdotal reports suggest that simultaneous administration of almitrine, a pulmonary vasoconstrictor, or nitric oxide inhalation may enhance the positive effects of ventilation perfusion matching. It will take a larger placebo-controlled trial to determine if additional benefits can be obtained from this drug. Liposomal PGE_2 has also been studied in randomized clinical trials. There were no improvements in survival or ventilator time associated with this therapy. (presented by Edward Abraham, American College of Chest Physicians, New Orleans, LA, October 30, 1997.)

Anti-adhesion molecules: As data continue to accumulate on the mechanisms by which leukocytes adhere to endothelium as a pre-requisite to tissue migration, approaches to the inhibition of this process have become

apparent. Adhesion mechanisms in the lung differ from those in the systemic circulation making data from studies of the latter difficult to extrapolate to the lung [117]. There are now a variety of agents, most commonly blocking antibodies (humanized monoclonals) to these adhesion systems, which have been shown to be of benefit in animal models and will soon be available for clinical trials.

Proinflammatory approaches: There is increasing evidence that agents which increase the inflammatory response may prevent the development of ALI/ARDS. The suggested mechanism is that of reducing or containing infection so as to prevent a more generalized inflammatory response that can injure the lung. The only clinical studies conducted thus far have been with granulocyte-macrophage colony stimulating factor (GM-CSF) [118].

Surfactant replacement therapy: Surfactant apoproteins are important in preventing surfactant inactivation in the inflamed lung and in promoting biophysical function. Studies are now focused on developing synthetic surfactants that contain apoproteins or apoproteins analogs that confer these properties. The mode of surfactant delivery to the lungs is potentially important. In treatment of neonates with Respiratory Distress Syndrome and in animal studies, bolus administration to the tracheobronchial tree is often used. In adults, large volumes required for bolus administration are exceedingly costly. Techniques to optimize distribution require further study [42,76,119]. At least one large scale trial of a synthetic surfactant failed to show benefit, possibly on the basis of inadequate aerosol deposition [77]. Yet other studies with different agents suggest benefit [75,82].

Gene therapy: The science of molecular biology has advanced considerably in the last several years such that therapeutic interventions with DNA are now technically feasible. There have been some clinically relevant early successes in the application of these techniques in animals. Examples include the transfection of the genes for alpha1-antitrypsin, manganese superoxide dismutase, and prostaglandin G/H synthase [120]. Transfection of these genes into humans are in early phases of investigations. Many unanswered questions remain regarding such issues as localization as well as mechanisms for activation and de-activation of transfected genes.

Recommendations and future research

Part I of meetings of the American-European Consensus Conference [4], indicates that mechanistic prioritization of pharmaceutical interventions is not possible at

this time. However, the committee felt that clinical research should be aggressively pursued in this area of human disease and that this research would be fostered by the following:

1. Development of a network of committed, experienced clinical investigators with the scientific expertise and clinical resources to systematically evaluate new therapeutic agents in large scale clinical trials.
2. Enhancement of the mechanisms for communication between basic and clinical scientists collaborating in the development of clinical interventional strategies.
3. Working to insure that clinical trials fully investigate the mechanism of response to new therapies employing cellular, molecular and physiological criteria.
4. Defining and validating physiologic endpoints which quantitate morbidity and resource utilization.
5. Continue the systematic pre-clinical and clinical evaluation of the therapeutic modalities which seem reasonable based on pre-clinical study.

Subcommittee III: general supportive care

Background

When all the outcome studies of patients with the ARDS are examined collectively and over time, it appears as if mortality has decreased since original description 30 years ago [2,51,121]. In part, this improved survival may reflect increased awareness of the factors inducing ALI and their correction prior to the clinical appearance of the syndrome. One would also presume that mortality would decrease with the use of more aggressive patient monitoring, care and treatment, improved non-ventilatory organ system support, and more potent antibiotics.

Controversies

Oxygen delivery: The present literature reflects significant differences in opinion as to which level of global oxygen delivery (DO_2) should be suggested for patients with pre-existent ALI [122, 123]. Indeed, recent data [55,124] and meta-analysis of several studies [125] suggests that non-specific augmentation of DO_2 to improve patient outcome is not beneficial. Furthermore, significant differences exist as to the method of cardiovascular support as it relates to intravascular fluid replacement [126,127] and the infusion of vasoactive drugs [128,129] to either maintain or improve DO_2 . However, the committee felt that there can be no target level of global DO_2 adequate for all patients with ALI. This is because of the complex relations between global blood flow, regional blood flow, tissue oxygenation, and local meta-

bolic demand. Furthermore, because of these complex interactions and the co-existence of associated organ system dysfunction, it would not be possible to define an optimal left ventricular filling pressure, minimal or optimal hemoglobin and hematocrit, or choice of fluid (crystalloid or colloid) replacement therapy to be used universally [130]. However, attempts at standardization of therapy based on pathophysiological principles and clinical data are important in order to maximize risk to benefit ratios and also to assess efficacy in clinical trials. Furthermore, clinical studies should carefully define both the measured cardiovascular status of their patients and what, if any, therapeutic end-points were used to titrate cardiovascular support.

Cardiovascular support: There is little controversy that cardiovascular instability should be corrected rapidly with fluid replacement and/or vasoactive therapy in order to maintain adequate organ perfusion. However, the exact levels to which cardiovascular variables need to be manipulated likely depends on the individual patients and associated disease states. A primary goal of these measures is to maintain O₂ availability to the tissues at appropriate levels.

Certain caveats appear to be clinically relevant. The persistence of a positive fluid balance is associated with a poor prognosis [131]. In those patients in whom the accurate and continued assessment of cardiovascular status is required, there is a place for the use of invasive hemodynamic monitoring at the present time. This is a highly controversial topic which has been addressed in detail elsewhere [132,133]. However, the specific type of monitoring should be individualized and no uniform rules for its application are generally accepted. Trends in hemodynamic variables in response to therapy and over time are as important as absolute values of these variables.

Infection control and indwelling catheters: Appropriate hospital hygiene and the standard use of sterile techniques are of fundamental importance in the prevention of nosocomial infection. Current practice regarding the routine replacement of vascular catheters is variable. Recent evidence suggests that routine replacement of vascular catheters, in the absence of sepsis, is not necessary [134]. The routine changing of endotracheal tubes after a defined interval is not recommended. The supine position is a risk factor for pulmonary superinfection [135]. Although prevention of nosocomial infection is a goal of supportive therapy, there are no definitive data to indicate that a reduction in nosocomial pneumonia decreases mortality. Selective decontamination of the digestive tract (SDD) or trachea decreases the incidence of tracheal colonization with bacilli and fungi [136]. However, the ability of these treatments to reduce mortality in patients with ALI has not been demonstrat-

ed. Furthermore, routine use of intravenous antibiotic prophylaxis in the non-immunocompromised patients is not justified. Continuous subglottic aspiration is an excellent non-antibiotic prophylactic strategy to reduce the incidence of early ventilator-associated pneumonia [137]. Antibiotic therapy should be guided by bacteriologic culture results whenever possible. It is important to recognize that fever can be of a non-infectious origin. Cultures of reliable specimens should always be taken prior to initiating empiric therapy for presumed infection. In the microbiologic diagnoses of pneumonia, protected brush specimens or BAL using quantitative cultures with thresholds of 10³ colony-forming unit per milliliter (cfu/ml) and 10⁴ cfu/ml, respectively, appear to be useful guidelines [138], but are not the only way of establishing the diagnosis [139]. These methods can be used by bronchoscopic guidance or blindly, though the yield of pure cultures tends to be higher with guided sampling of the lower respiratory tract. However, the effect of prior antibiotic treatment on the sensitivity and specificity of these culture techniques is not known [140].

Nutritional support: Although it is essential to provide nutritional support to all patients who have a prolonged course in the ICU, reliable measures of the adequacy of nutritional support in the critically ill patient remain elusive. Nutritional supplementation should be attempted in all patients after a few days of critical illness because of its association with a more favorable outcome [141, 142]. All three nutritional constitutions, carbohydrates, lipids and protein, should be given. However, the specific caloric requirements and ratio of carbohydrates lipids and protein has not be defined. Trace elements and vitamins should be included in nutritional support. In general, in the acutely ill patient it may be inappropriate to attempt to match the patient's metabolic capabilities as such strategies can induce liver dysfunction, volume overload, and hyperglycemia [143]. Whenever possible, feeding should be by the enteral route. Enteral alimentation decreases the incidence of gastric colonization with gram negative bacilli, stress ulcers and mucosal atrophy. The maintenance of enteral nutrition may have important effects on the host immune response. In particular, the measurement of nitrogen balance is not useful in decision making in this setting [144].

Non-pulmonary organ support: Cardiovascular support is described above. The appropriate maintenance of cardiovascular function and the use of enteral alimentation are the only proven means to maintain or improve gut function. The methods readily available to assess hepatic function are often non-specific and confounded by treatment and disease states. The routine use of dopaminergic agents to maintain renal blood flow and function

is an unproven therapy [145]. Maneuvers which increase intracranial pressure, such as PEEP [146], respiratory therapy and certain body positions, may decrease cerebral perfusion pressure and impair cerebral function [124]. At present, there are no data to support the routine use of hemofiltration, except specifically for renal dysfunction support, in the patient with ALI. The use of hemofiltration to clear circulating inflammatory mediators deserves additional study and is not recommended.

Most critically ill ventilator-dependent patients need sedation and/or analgesia to improve patient comfort, facilitate ventilation, and permit sleep. Occasionally patients require paralytic drugs to control ventilator dyssynchrony and reduce oxygen demand. Because of the short and long term paralytic risks associated with such treatment, usage of these agents should be limited to the briefest period possible and patients should be monitored closely to minimize the depth of paralysis induced [147]. However, the commonly used agents may carry significant complications. Prolonged paralysis is now a recognized complication of sustained use of paralytic agents and narcotics can impair gut motility thus necessitating intravenous feedings [94]. Changes in body position facilitates bronchial toilet, gas exchange and minimizes skin problems [148]. The routine use of anti-thrombotic therapies is recommended. Routine stress ulcer prophylaxis is probably useful, however differences exist in the efficacy and side effects with different therapies. Specifically, sucralfate has been shown to be superior to either ranitidine or antacid therapy for preventing late onset pneumonia in ventilated patients [149].

Recommendations

In the absence of clear data with which to develop guidelines for the general support of patients with ALI/ARDS, the following basic recommendations were proposed by the committee. It was felt that since the quality of care is a primary determinant of outcome, the following general supportive methods be used:

1. It is important to maintain hemodynamic stability for the overall outcome of the patient. However, beyond this, it is difficult to define what the target levels of cardiovascular support should be and the methods by which these levels should be achieved. The committee understands that such a schema does not ensure that tissues will be able to utilize this oxygen and other nutrients delivered to them.
2. Invasive monitoring need not be present in all patients or in a given patient throughout the clinical course, but used only as long as needed for adequate assessment of the cardiovascular status.

3. Focus care at preventing infection as well as locating the source of existent infections and eradicating these. Maintenance of adequate nutrition, preferably enteral, and other non-pulmonary organ function, merit as much concern and care as do ventilatory management and other ALI/ARDS-specific therapies.

Future investigations

Considering the importance of general supportive care in determining outcome from critical illness, it is recommended that prospective studies investigating specific aspects of general supportive care be undertaken in this patient population. Without such data we are limited to making empiric recommendations based on traditional clinical practice. Accordingly, attention to details related to nursing support, monitoring, and related factors need to be addressed. Since ALI/ARDS is often a local manifestation of a systemic process, therefore it should be considered within the context of overall clinical care when any specific therapeutic strategy is assessed [130]. In addition, variations in general supportive care strategies in different institutions make comparisons of results of clinical trials difficult. To minimize these differences, the committee suggests that all the suggested clinical investigations proposed below include common minimal standards of care.

1. Compare effects of different targeted levels of cardiovascular support and methods of attaining these levels (pharmacologic vs. fluid resuscitation) on global and organ-specific function relative to acute mortality and long-term outcome.
2. Compare effects of different therapies (such as selective decontamination of the digestive tract, continuous veno-venous hemofiltration with dialysis) on the level of intravascular inflammation, lung function and outcome of ALI.
3. Compare different strategies which aim to prevent gut dysfunction (SDD, enteral alimentation, and type of stress ulcer prophylaxis) for their ability to minimize nosocomial pneumonia, intravascular inflammatory responses, lung dysfunction and outcome in patients with ALI.
4. Compare cost-effectiveness of various forms of supportive therapy on outcome of ALI.
5. Establish better methods to assess the adequacy of cellular oxygen availability based on regional organ-system function.

Subcommittee IV: resolutions and remodeling after acute lung injury

Background

Physiology and pathology of acute lung injury: In the initial phase of ALI, all patients have a severe defect in oxygenation, a reduction in lung compliance, and bilateral pulmonary infiltrates [150–152]. During this early phase (approximately the first 3–5 days of respiratory failure), there is conclusive evidence for an increase in permeability of the endothelial and epithelial barriers of the lung with accumulation of protein-rich edema fluid in the interstitium and air spaces of the lung [153–155]. In some studies, there has been evidence for the production of abnormal surfactant or inactivation of surfactant, perhaps in part by the protein-rich edema fluid in the air spaces of the lung [156,157]. The edema fluid contains a variable quantity of red blood cells, white blood cells (neutrophils, monocytes, and lymphocytes), hyaline membranes (which consist of albumin, immunoglobulin, fibrin, fibrinogen and other proteins) [72, 158–160]. Often, there is ultrastructural evidence of endothelial and epithelial cell injury, sometimes with frank necrosis of alveolar type I epithelial cells [159]. Pathologically, this constellation of pulmonary abnormalities has been termed diffuse alveolar damage.

Clinically, there is considerable heterogeneity in the subsequent course of patients with ALI. Some patients recover from the severe permeability pulmonary edema within the first 7 days without progressing to a sub-acute or chronic phase of lung injury [161]. There are other patients, however, who enter a sub-acute phase of lung injury that develops about 5–7 days after the onset of ALI [150,151]. This phase is characterized physiologically by several features: 1) an increase in alveolar dead space, necessitating a high minute ventilation to achieve a normal or near normal PaCO₂; 2) a persistently decreased lung compliance, thus requiring the use of higher than normal airway pressures for ventilation; and 3) a persistent oxygenation defect. In this phase, the alveolar-arterial oxygen difference may stabilize or modestly improve, although usually there is still the need for a moderate- to high-fraction of oxygen and positive end-expiratory pressure (PEEP) to maintain adequate arterial oxygenation. Radiographically, there are usually persistent, largely unchanging bilateral infiltrates. Pathologically, there is evidence of interstitial fibrosis with proliferation of alveolar type II cells and both obstruction and destruction of portions of the microcirculation of the lung [159, 160–164].

Finally, in some patients in whom respiratory failure persists beyond 14 days, there is a gradual transition to a chronic phase of lung injury with persistently low lung compliance and a markedly elevated dead space fraction (> .60) that requires a high minute ventilation

to maintain a normal or near normal arterial carbon dioxide tension. Pathologically, this chronic phase is characterized by extensive pulmonary fibrosis with obliteration of normal alveolar architecture and progressive development of emphysematous regions of the lung including the development of discrete bullae that can be appreciated on computerized axial tomography [159,160,163,164].

Definition of the resolution phase of acute lung injury: During recovery from ALI, the increased permeability of the endothelial and epithelial barriers must be sufficiently resolved for net fluid clearance from the lung to be possible. Then the process of recovery must begin with clearance of at least some of the edema fluid that has accumulated in the interstitial and alveolar spaces of the lung [154]. Resolution must also include the process of clearing the soluble and insoluble protein that has extravasated into the interstitium and air spaces of the lung [164–167]. The early repair process also involves re-epithelialization of the injured alveolar barrier initially, at least, with proliferating alveolar type II cells [159,160,168].

At the same time, there is a pathological proliferation of fibroblasts often associated with the deposition of excessive quantities of extracellular matrix, particularly collagen, that contributes to the poor lung compliance and loss of normal alveolar architecture [164,168]. This phase of ARDS has often been termed the fibroproliferative response that occurs in some patients following ALI [152,169,170]. The resolution of this fibrosing alveolitis requires further remodeling of the lung with gradual resolution of the pulmonary fibrosis and restoration of normal alveolar-capillary lung units [159,160,171,172]. Physiologically, this phase of lung remodeling can be appreciated by a gradual improvement in lung compliance and a decline in minute ventilation that parallels a reduction in alveolar dead space [150,173].

The importance of a restored alveolar epithelial barrier in the process of recovery from ALI has been recognized in morphological studies [159, 160,174] as well as in a recent study of the functional capacity of the alveolar epithelium to remove excess fluid from the injured lung [154]. The mechanism for alveolar fluid clearance depends on active sodium transport and requires a predominantly intact epithelial barrier [161,175,176]. Also, intact alveolar epithelial type II cells are required for normal surfactant production. An intact epithelial barrier is probably important in providing the basis for repair of the injured lung, although the complex interaction required for lung remodeling involves endothelial cells, epithelial cells, fibroblasts, alveolar macrophages, extracellular matrix, coagulation factors, cytokines and growth factors. The mechanisms that regulate and coordinate the repair are poorly understood. For example,

the molecular and cellular signals that halt excessive deposition of collagen need to be identified [169]. The factors that contribute to the gradual but progressive regression of pulmonary fibrosis and restoration of normal lung alveoli over weeks to months also need to be better understood [177, 178]. In addition, the mechanisms that control regeneration and recanalization of the microcirculation of the lung are poorly understood. Progress in understanding the growth and development of the fetal and newborn lung may provide an important model for studying the recovery of the adult lung after development of ALI.

Controversies

Quantification of resolution: While recovery from ALI can be well described on the basis of several physiologic and morphologic studies in both patients and experimental animals, the best methods for detecting the onset of the resolution phase are not well defined. In order to provide guidelines for evaluating the resolution of ALI, we will briefly discuss 1) the use of pulmonary physiologic parameters; 2) biological markers that require measurements in the plasma and pulmonary edema fluid, or bronchoalveolar lavage fluid from patients with ARDS; and 3) indices of nonpulmonary organ dysfunction.

1. Pulmonary physiological indices of lung function: The traditional indices of gas exchange and respiratory compliance have limitations [151,152]. For example, an improvement in arterial oxygenation may reflect clearance of some of the pulmonary edema [154,179]. However, improved arterial oxygenation may also occur simply because of changes in ventilatory support (e.g. higher levels of PEEP), not necessarily because of an improvement in lung function. Similarly, the chest radiograph may show signs of resolution of edema in some patients, but radiographs that are done in the intensive care unit may be insensitive to small changes because they are portable films and frequently not well standardized in terms of the patient's position or the distance and angle at which the radiographs are obtained. There may be more aeration on one film compared to another radiograph simply because higher levels of PEEP have increased lung volume. An improvement in lung compliance as reflected by either a decline in the mean airway pressure or a lower plateau airway pressure can be a sign of improved lung distensibility; however, small changes in the tidal volume, inspiratory flow rates, or the level of positive end-expiratory pressure (PEEP) can result in better indices of lung compliance without necessarily indicating an objective improvement in lung function. The need for less PEEP can be a reasonable index of improvement provided that the conditions of ventilation have not been substantially altered and

that static compliance of the lung is also improving. The dead space fraction is a sensitive method for detecting the fraction of the alveolar space that is not perfused. It can also be a particularly useful index of the magnitude of lung injury as the patient's lung injury evolves from the acute to the sub-acute and the chronic phases of the disease [150]. The resolution of the acute phase of protein-rich pulmonary edema often occurs in parallel with some improvement in the patient's minute ventilation as well as the airway pressure needed for positive pressure ventilation. This physiologic pattern probably occurs because of the fibrosing alveolitis that is associated with obliteration of portions of the pulmonary microcirculation [150,152]. The fibrosing alveolitis is part of the pathophysiology of this sub-acute phase of lung injury, but it may also be a first, although imperfect, step in remodeling of the lung following ALI [160,169].

2. Biological indices of pulmonary function: There are several biological indices of lung function that may prove useful in assessing the recovery from ALI/ARDS. As discussed above, the clearance of some of the alveolar edema fluid constitutes good evidence that the alveolar barrier is functional and that net reabsorption of alveolar fluid exceeds edema formation. Measurement of total protein concentration in sequential samples of alveolar edema fluid can provide an index of the capacity of the alveolar barrier to remove edema fluid, although this method has not been validated in large numbers of patients at different medical centers [154, 176].

Bronchoalveolar lavage (BAL) of the air spaces of patients with ALI/ARDS has generated several interesting and potentially important markers and mediators of inflammatory lung injury. For example, in edema fluid and BAL samples, markedly elevated levels of interleukin-8 (IL-8), an important chemotactic and pro-inflammatory cytokine, has been associated with a higher mortality in patients with ALI/ARDS [70] as well as in patients at risk of ALI/ARDS [71]. Biological markers in the air spaces of the lung of endothelial and epithelial cell injury or specific cell adhesion molecules may also provide information regarding the extent and mechanisms of ALI/ARDS, as well as provide information regarding prognosis and resolution [70,71,180]. A recent report indicates that measurement of type III procollagen (PCPIII) peptide in bronchoalveolar lavage (BAL) fluid of patients with ARDS at days 3 and 7 may provide a predictor of nonsurvival, perhaps in part because PCPIII reflects ongoing pulmonary fibrosis following ALI [158]. Lower levels of PCPIII were associated with a better prognosis for survival, especially when combined with a physiologic index of resolving lung injury. A recent study of this marker in the edema fluid of patients with ARDS confirms its potential value as an early marker of fibrosing alveolitis and its potential prognostic value [180]. Abnormalities in surfactant se-

cretion or inactivation of surfactant by serum proteins in the alveolar spaces in ALI may be a good marker of lung injury [156,157], but current research techniques do not allow determination of surfactant secretion and turnover in the remodeling phase of ARDS. It is now possible, however, to measure surfactant proteins in pulmonary edema fluid, BAL, or plasma [181].

3. Non-pulmonary organ dysfunction: Several clinical studies of patients with ARDS have emphasized that survival is closely linked to both nonpulmonary organ failure and recurrent infection [182–184]. For example, when the initial clinical disorder associated with the development of ALI (such as sepsis or severe trauma) results in nonpulmonary organ failure, then the resolution of ALI may not occur until the nonpulmonary organ failure resolves. Also, there is evidence that patients with nonpulmonary organ failure have a higher likelihood of developing ARDS, emphasizing again that the development and resolution of ARDS must be studied and evaluated in the context of both pulmonary and nonpulmonary organ failure. Therefore, studies of the recovery from ALI should include data regarding the presence or absence of ongoing nonpulmonary organ failure as well as information regarding unresolved pulmonary and nonpulmonary infections.

Recommendations

In order to address the best means of detecting and defining the onset of resolution or recovery from ALI, the committee recommends the following methods:

1. Clinical conditions for evaluating ALI: Acute lung injury must be evaluated in the context of systemic factors. For example, the most reproducible data will be those obtained at a time when the patient is hemodynamically stable and in the absence of clinical signs of sepsis. Indices of nonpulmonary organ function should be obtained. It is not clear currently whether or not inclusion of a formal severity of illness score will be useful or necessary.
2. Gas exchange: A stable or improving $\text{PaO}_2/\text{FiO}_2$ ratio with the same level of positive end-expiratory pressure (PEEP) for 24 hours constitutes one practical guideline that the ALI is stable. If oxygenation improves for another 24 hours, this finding is an indication that the resolution of the lung injury has begun. Similarly, reductions in physiologic deadspace estimated from direct measurements of PCO_2 and minute ventilation provide evidence that resolution has begun.
3. Airway pressures: Peak and mean airway pressures, as well as the difference between the peak and the end-expiratory airway pressure which are stable or improving for 48 hours, indicate the sub-acute and more chronic phases of the injury have reached a plateau, and the

patient may now be entering the recovery phase. Ultimately, the ability to tolerate unassisted ventilation is the critical functional end point of recovery from ALI.

4. Infection: The failure to resolve and prevent secondary infections is a major explanation for non-resolution and non-survival in ALI.

Future research

It seems logical to conclude that the onset of the resolution of alveolar edema in ARDS patients constitutes the first step in recovery from ALI. However, the resolution of alveolar edema is not sufficient to guarantee recovery since some ARDS patients who progress to the sub-acute and chronic phases of ARDS have persistent respiratory failure primarily because of pulmonary fibrosis and obliteration of functional alveolar-capillary lung units, not simply because of persistent pulmonary edema. Nevertheless, it is still reasonable to conclude that the clearance of some of the excess alveolar edema fluid in patients with ARDS indicates a first step in the resolution process, even if the clearance of some of the excess alveolar fluid does not predict recovery in all patients.

The research questions relevant to developing a better understanding of lung edema resolution and remodeling are:

1. Can edema fluid clearance be enhanced through use of exogenous beta adrenergic agonists or catecholamines? Since active sodium transport by alveolar type II cells is now established as the primary mechanism driving reabsorption across the alveolar epithelium, it is necessary to know if this process can be accelerated in patients with ALI and whether this improves outcome [176,185, 186].
2. Which mechanisms can potentiate the formation of a functional, new alveolar epithelial barrier and the reconstitution of an extracellular matrix conducive to both limiting excessive collagen deposition and recanalizing the lung microcirculation?
3. What is the sensitivity and specificity of the proposed clinical indices of oxygenation ($\text{PaO}_2/\text{FiO}_2$ and the level of PEEP or auto-PEEP) plus the indices of carbon dioxide excretion (minute ventilation and PaCO_2) and decreased lung compliance (rising peak and mean airway pressure and the difference between the peak and end-expiratory airway pressure) for identifying the stages of lung injury in the acute and sub-acute phases of the disease.

Subcommittee V: definitions and strategies for the design and coordination of studies between centres and continents

Background

The definitions and goals of efforts to coordinate clinical studies have been presented previously [1]. They include: (a) development of common databases, (b) standardization of study methods, (c) facilitation of study of therapeutic modalities, and (d) epidemiologic description of ARDS. While we realize these goals will only be achieved gradually, we believe there are certain initial steps that should be taken now [4].

Controversies

Current data on the prevalence, distribution (both geographic and by type of hospital) and natural history of ARDS are inadequate. Further, it is likely that the estimate of 150,000 cases of ARDS/year in the USA [1,2] is inflated. This estimate, which translates to 65 cases per 100,000 population, contrasts with estimates of 4.5 and 3.5 cases per 100,000 in the U.K. and in the Canary Islands, respectively [187,188]. In collecting epidemiologic data, it will be useful to record for consecutively observed patients: (a) information relating to etiology (at a minimum, direct or indirect cause of lung injury); (b) mortality, including cause of death when possible, and whether death was associated with withdrawal of care; (c) presence of failure of other organs and other time-dependent covariates; and (d) follow-up information including fraction of patients for which such data are available, recovery of lung function, and quality of life.

The collection of epidemiologic data should be based on clear definition [4], as well as on a system that stratifies severity of ALI. The severity of ALI and the associated clinical features can be assessed by the lung injury score [151,189,190] or by the Apache III or SAPS II scoring systems [191]. For investigative purposes, it is important to take into account additional factors that affect prognosis, which may be present initially or which may develop during the evolution of the disorder. The most important of these are incorporated into the GOCA stratification system (Table 1). This score is not designed to predict outcome, but could be used to simply and succinctly present important clinical information. In the past, many investigators have used the term acute respiratory distress syndrome to describe the most severe forms of ALI. The proposed stratification system deals with the entire continuum of ALI, and incorporates additional factors that have an important influence on prognosis.

Epidemiologic studies will require participation of investigators trained in sophisticated epidemiologic

Table 1 Stratification system of acute lung injury

Letter	Meaning	Scale	Definition
G	Gas exchange (to be combined with the numeric descriptor)	0	PaO ₂ /FiO ₂ ≥ 301
		1	PaO ₂ /FiO ₂ 201–300
		2	PaO ₂ /FiO ₂ 101–200
		3	PaO ₂ /FiO ₂ ≤ 100
		A	Spontaneous breathing, no PEEP
B			Assisted breathing, PEEP 0–5cm H ₂ O
		C	Assisted breathing, PEEP 6–10cm H ₂ O
		D	Assisted breathing, PEEP ≥ 10cm H ₂ O
O	Organ failure	0	Lung only
		1	Lung + 1 organ
		2	Lung + 2 organs
		3	Lung + ≥ 3 organs
C	Cause	0	Unknown
		1	Direct Lung Injury
		2	Indirect Lung Injury
A	Associated Diseases	0	No coexisting diseases that will cause death within 5 years
		1	Coexisting disease that will cause death within 5 years but not within 6 months
		2	Coexisting disease that will cause death within 6 months.

techniques and clinical cost estimation. Particular attention will be required to allow description of the prevalence of ARDS within a defined geographic area, since the definitions used for ARDS are not standardized and common coding practices that record cases of ARDS do not exist. Funding for epidemiologic studies and availability of other resources should be explored. Sources may include the World Health Organization, European Community and National Institutes of Health.

Concurrent with study of the epidemiology of ARDS, efforts to coordinate and/or facilitate study of various therapies for ARDS should go forward. While information from the Consensus Conference may suggest several potential clinical interventions, the Committee believes that investigator-initiated studies will be a major vehicle of progress. To facilitate such studies, the Committee recommends collecting, collating, and making widely available information supplied by investigators who are interested in participating in clinical studies.

However, as this group accumulates "property" (e.g., lists of interested investigators), issues related to value of the property and liability for misuse of the property become evident. Thus, it is suggested that recommenda-

tions of the Committee should be enacted by established incorporated professional societies.

As pharmaceutical companies develop prospective interventions that may be of value in treating patients with ARDS, it is useful to have in place an advisory group to provide independent comment on the merits of the proposed intervention and who might facilitate cooperation between industry and clinical investigators. These functions have value, and for reasons cited above, might be best managed within the structure of established professional societies.

Recommendations and future research

1. Interested professional societies should be encouraged to collaborate on developing mechanisms for the design and study of the incidence, distribution, natural history, cost and outcome of ARDS.
2. These societies should be encouraged to collaborate on collecting, collating, and making available information about investigators interested in participating in clinical trials.
3. Appropriate societies should establish an interface with the pharmaceutical industry to provide consultation and to facilitate industry interaction with clinical investigators.
4. Progress in these areas should be systematically reported through standard society mechanisms.

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