Centennial Review

Acute Respiratory Distress Syndrome A Historical Perspective

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Though well described even in ancient writings, the acute respiratory distress syndrome (ARDS) gained major medical attention with the availability of mechanical ventilation and establishment of intensive care units. In the 50 years since this beginning there have been remarkable advances in the understanding of the etiology, physiology, histology, and epidemiology of this often lethal complication of common human maladies. Until recently, improvements in outcome have mainly followed improvements in intensive care unit operation and their associated life support systems, and have not come through discoveries made in the course of prospective randomized trials. In spite of the remarkable increase in research focused on ARDS, there remain a large number of unanswered clinical questions that are potentially extremely important with regard to short-term morbidity as well as long-term outcome. The ARDS Clinical Trials Network study of tidal volume has proven that randomized trials in ARDS with positive results are possible even when using difficult primary outcome measures such as mortality or ventilator-free days. Therefore, the rich combination of new trial strategies, potential treatments, experienced investigators, and increasingly standardized routine care set the stage for rapid advances to be made in the short- and long-term outcomes of this devastating syndrome.

Keywords: acute lung injury; acute respiratory distress syndrome; adult respiratory distress syndrome; noncardiogenic pulmonary edema

One hundred years is not long in the context of medical history, but for the acute respiratory distress syndrome (ARDS), this period encompasses nearly every important event related to its physiology, incidence, and treatment. The advances made even in the past 50 years are staggering when compared with all else that came before. For many physicians practicing today, it is difficult to remember a time before intensive care units and mechanical ventilators. This article will provide a brief history of the development of the current concepts regarding the pathophysiology of ARDS, a summary of current management options, and a brief discussion of future directions.

ARDS: THE EARLY HISTORY

There are many interesting historical events that correlated with or impacted the identification and management of ARDS leading

to the most current concepts. These events set the stage for the critical care revolution that occurred in the last half of the twentieth century (Table 1).

In 1821, in what was probably the first published scientific description, Laennec described the gross pathology of the heart and lungs and described idiopathic anasarca of the lungs; pulmonary edema without heart failure in "A Treatise on Diseases of the Chest" (16). By the 1950s, pulmonary edema had become a medical subject heading by the National Library of Medicine; however, no distinction was made at that time between cardiac and noncardiac causes. But what clearly moved ARDS from a nearly universally fatal form of "double pneumonia" was the development of methods of establishing secure airway access using tubes that could be attached to mechanical ventilators to deliver adequate pulmonary distending pressures (6). These techniques extended the lives of these patients from a few hours to many days or even weeks—long enough to recover in some cases. As this new kind of patient began to populate the newly established intensive care units, their condition rapidly became recognized as one of the most challenging acute clinical processes to treat. Since acute, diffuse, and dense bilateral infiltrates were almost never observed except in patients requiring prolonged mechanical ventilation, many surmised the cause of such infiltrates was the ventilator, hence the term "respirator lung" (17).

For a period of time ARDS went by the name of inciting injuries (e.g., DaNang lung, shock lung, post-traumatic lung, etc.). It wasn't until 1967, in a landmark article published in *Lancet*, that Ashbaugh, Bigelow, Petty, and Levine first described the clinical entity that they called "acute respiratory distress in adults" (11). This article recognized for the first time that ARDS was a constellation of pathophysiologic abnormalities common to a relatively large number of patients but that were initiated by a wide variety of unrelated insults—for example, gastric aspiration, sepsis, blunt trauma, near-drowning, etc. Interestingly, the difficulty in making the diagnosis remained evident in that at least five of the patients studied could have had ARDS secondary to or complicated by fluid overload. Also notable in this 1967 report, ARDS was "acute" respiratory distress syndrome. However, in 1971 Petty and Ashbaugh used the term "adult" respiratory distress syndrome in another publication (18), probably to address the perception of ARDS as an adult version of the previously described infant respiratory distress syndrome (IRDS).

In 1992 the American European Consensus Conference (AECC) was charged with developing a standardized definition for ARDS to assist with clinical and epidemiologic research. The AECC recommended that a new designation, acute lung injury (ALI), be defined as "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension" and "is associated most often with sepsis

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syndrome, aspiration, primary pneumonia, or multiple trauma and less commonly with cardiopulmonary bypass, multiple transfusions, fat embolism, pancreatitis, and others.” Acute (not adult) respiratory distress syndrome was defined as a subset of ALI patients with more severe oxygenation defect. ALI and ARDS are acute in onset and persistent, associated with one or more known risk factors, and are characterized by arterial hypoxemia resistant to oxygen therapy alone and diffuse radiologic infiltrates (19). Table 2 presents the three most commonly used definitions.

In the decade of the 1970s ARDS became increasingly recognized, but hydrostatic causes (e.g., volume overload) were difficult to rule out. The potential for confusion was so great that measurements of pulmonary artery wedge pressure became a very common means of diagnosis (21). In fact, entry criteria for one of the earliest randomized trials of corticosteroids required a measured pulmonary wedge pressure less than 19 mm Hg (22). This once nearly routine measurement is now much less frequent with the realization that exceeding an arbitrary pulmonary artery occlusion pressures (PAOP) does not exclude the diagnosis of ALI, and that there are usually other clinical data and historical clues that allow a fairly secure diagnosis of ALI apart from volume overload to be made. Even when the PAOP is less than 18 mm Hg, one cannot be certain that edema is the result of altered permeability. Reduced colloid oncotic pressure as observed in hypoalbuminemic states promotes edema in the absence of permeability changes (23–25).

Lung dysfunction secondary to direct insults to the lung, for example, aspiration (primary ARDS), may be different from lung injury from extrapulmonary origin, for example, sepsis (secondary ARDS). This is an interesting concept, and some clinical markers that differentiate the two have been described. But work is still underway to determine implications for patient management (26). The differential diagnosis of ARDS using the

AECC definition, is significantly broad that the resulting list of other potential confusing diagnoses is limited to diseases that appear similar with regard to chest radiography and oxygenation defect, but are subacute or chronic: interstitial or idiopathic pulmonary fibrosis, lymphangitic carcinoma, pulmonary veno-occlusive disease; or are due to increased hydrostatic pressures: mitral stenosis, left ventricular failure, intravascular volume overload (19). Thus the diagnosis of ARDS is inclusive and indeed can coexist with other more specific diagnoses such as pneumococcal pneumonia (27).

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Prior to the 1960s, ARDS was characterized histologically at the light microscope level as a diffuse neutrophilic alveolar infiltrate, with hemorrhage, and the accumulation of a protein-rich pulmonary edema (28). In the late 1970s, there was intense focus on the role of neutrophils as an important component of the inflammatory response in ARDS. More recently, experimental models have shown that pulmonary neutrophils demonstrate increased activation of the transcriptional regulatory factor NF- κ B and produce increased amounts of the proinflammatory cytokines whose transcription was dependent on NF- κ B, including tumor necrosis factor and the kinases p38 and PI3-K. In humans, neutrophils demonstrate the same patterns of expression in response to LPS or other stimuli. Although it appears that activated neutrophils play a central role in the development of lung injury, their relative importance in critically ill patients remains to be determined (29).

In the 1980s an “exudative” phase, associated with a panoply of cytokines (e.g., tumor necrosis factor and interleukin (IL)-1 and -8) was thought to serve as an inciting and sustaining factor in the intense inflammation observed in these lesions. The relative cytokine concentrations and their role in alveolar lining fluid is still under investigation (30, 31). Increased oxidant stress and protease activity in the alveoli decreases surfactant production, and inactivates remaining surfactant thereby promoting widespread atelectasis. In addition, elastases damage the structural framework of the lung. In the 1980s, ultrastructural analysis revealed both alveolar capillary and epithelial cell injury in ARDS (32) that exacerbated the tendency for alveolar flooding and impairing fluid clearance.

Though long recognized that platelet activation and aggregation, microthrombi, and even intraalveolar deposition of fibrin were major components of the histologic appearance of ALI (33), it was not until the 1990s that the role of the coagulation system began to come into focus. A procoagulant tendency is observed as concentrations of anticoagulant proteins (protein C and S) fall and there is increased expression of procoagulant proteins (tissue factor) and antifibrinolytic proteins (plasminogen activator inhibitor-1) (34–38). Together these changes are probably responsible for thrombosis observed in alveolar capillaries as demonstrated by pulmonary arteriography (37) as well as in the alveolus itself (39). After the exudative stage, a prolonged phase sometimes referred to as fibroproliferative has been reported in some ALI patients during which chronic inflammation, fibrosis, and neovascularization occur (40). Unfortunately there are no features, except perhaps time that allow the clinician to distinguish these phases without a lung biopsy, an invasive procedure whose utility in the diagnosis and management of ALI is still being debated in the literature (40–44).

Macro-imaging has also provided valuable insights into the pathophysiology of ALI. The first reports of CT imaging of ARDS did not appear until the 1980s, demonstrating the infiltrative process in ARDS was more heterogeneous than initially believed. This finding led support to interventions such as volume

TABLE 1. MEDICAL EVENTS THAT MADE MODERN CRITICAL CARE POSSIBLE

Year	Progress
1896	Roentgen describes X-rays. Early chest X-rays required exposure time of 20 min and were not considered useful until the 1920s (1).
1929	Drinker and Shaw announce the invention of the iron lung during the polio epidemic (2)
1946	Fenn and coworkers publish work on pulmonary gas exchange, relating PO_2 , P_{CO_2} , respiratory exchange ratio, arterial O_2 saturation, alveolar ventilation, and altitude (3)
1950	Cortisone, first extracted in 1936, is used as a treatment for asthma (4)
1954	Clark develops an electrode for measurement of PO_2 , reflecting the level of O_2 in the blood (5)
1954	Ibsen first used cuffed endotracheal tubes and positive pressure ventilation (6)
1956	Forssmann and colleagues share the Nobel Prize in physiology and medicine for the advancement of right-heart catheterization. Their work led to the development of the Swan Ganz catheter (7, 8).
1959	Avery and Mead discover that some newborns' lungs do not produce surfactant (hyaline membrane disease, later called neonatal respiratory distress syndrome) (9)
1960	Moss and coworkers discover the benefits of chest compression to achieve artificial circulation (10)
1967	Ashbaugh and colleagues identify acute respiratory distress syndrome (11)
1960s	First developed in the 1950s, it was the late 1960s before intensive care units become common in the United States (12)
1976	Extracorporeal membrane oxygenation (ECMO) is introduced for neonates with persistent pulmonary hypertension, allowing the lungs time to heal (13, 14)
1978	Furchgott describes “endothelium-derived relaxing factor,” now known as nitric oxide. He was awarded the Nobel Prize for this work (15).

TABLE 2. THREE WIDELY USED DEFINITIONS OF ACUTE RESPIRATORY DISTRESS SYNDROME

Definition	Reference
Severe dyspnea, tachypnea, cyanosis refractory to oxygen therapy, decreased pulmonary compliance, diffuse alveolar infiltrates on chest radiograph, atelectasis, vascular congestion, hemorrhage, pulmonary edema, and hyaline membranes at autopsy.	Ashbaugh and colleagues, 1967 (11)
Four-point lung injury scoring system, specifies clinical cause of lung injury based on: Oxygenation, Positive end-expiratory pressure, Respiratory system compliance, and Chest radiograph involvement	Murray and colleagues, 1988 (20)
A three-criteria system including chest radiograph, oxygenation score, and exclusion of cardiogenic causes. Acute onset, bilateral infiltrates on chest radiography, Pulmonary-artery wedge pressure of < 19 mm Hg or the absence of clinical evidence of left atrial hypertension, and Acute lung injury considered present if $Pa_{O_2}/F_{I_{O_2}}$ is ≤ 300 and the ARDS subset was defined with a more severe oxygenation deficit, $Pa_{O_2}/F_{I_{O_2}} \leq 200$.	Bernard and colleagues, 1994 (19) (American European Consensus Conference Definition)

recruitment, prone positioning, and reduced tidal volume ventilation (45, 46).

EPIDEMIOLOGY AND INCIDENCE

Before the advent of intensive care, patients with ARDS did not live long enough for organized investigation. With better descriptors of the process of ARDS and the need to have a better understanding of the public health burden, the National Institutes of Health (NIH) organized a workshop in 1977 (47). Among other issues discussed was the estimated incidence of ARDS in the United States. By report of many of those who attended, the estimate of 150,000 cases per year in the United States was mostly just a guess, yet that figure has become widely cited. The actual incidence has now been approached more systematically and estimates range from about 15,000 to as high as 200,000 cases per year (48). A recent report by Luhr and coworkers (49) perhaps explains the problem involved in making precise estimates. These investigators found that among patients requiring mechanical ventilation for more than 24 h, for every patient with a diagnosis of ARDS there were roughly 10 other patients with hypoxemic respiratory failure. This latter group is very important from a public health perspective but is poorly described. It is likely that much of the variation in incidence rates relates to the difficulties in standardizing the radiologic diagnosis (48, 50).

MORTALITY

The advent of well-equipped ICUs, well-trained staff, and the availability of reliable positive pressure ventilators has allowed patients to be kept alive much longer and thus have the opportunity to heal the pulmonary injury and survive (11). Survival in ALI varies widely depending upon age, chronic disease burden, and nonpulmonary organ dysfunctions such as shock and hepatic failure. Younger trauma patients have the best outcomes (51, 52). Paradoxically, the initial degree of gas exchange impairment is a poor predictor of outcome unless severe (e.g., $Pa_{O_2}/F_{I_{O_2}} < 50$) (53). Persistent hypoxemia has greater predictive value (53, 54). Just two decades ago, ALI mortality was often reported to be 50 to 70% (9), but fortunately there has been improvement (51, 55, 56).

It is likely that advances in supportive care have decreased extrapulmonary organ failures and/or improved their support, for example, dialysis, accounting for the majority of the change (57). In the most recent randomized trials, overall 28-d mortality is 25 to 30%, while in surveys mortality ranges between 35

and 40% (58). Some data suggest the mortality of patients with ARDS persisting for greater than 1 to 2 wk may be far better than once thought and hovering at less than 30% (59–61). Though the predicted mortality of patients evaluated in early ARDS is well studied, mortality in patients with late (persistent) ARDS is much less well known. Based on ARDSNet data, it appears the long term survival of patients who make it to this stage, approximately 26%, is similar to the ARDS population overall (59). Figure 1 shows data from landmark studies providing observational evidence that ARDS survival is improving.

LONG-TERM MORBIDITY

In the 1970s and 1980s the major focus of concern for ALI survivors was the potential for persistence of lung function abnormalities such as impaired oxygenation and restrictive lung disease. But studies in the late '80s and early '90s revealed that lung function showed substantial recovery by 6 to 12 mo (63–65). Further gains in this regard may be seen now that lung-protective ventilation is being increasingly employed (66). It is now apparent that neuropsychiatric problems and neuromuscular weakness are frequent and often delay return to school or work for months and occasionally can be permanent (60, 67–71) (Figure 2).

These investigations have made it clear that as mortality continues to decline (51), our attention must be increasingly drawn to prevention of long-term disability. Persistent neuromuscular weakness and long-term, seemingly irreversible cognitive dysfunction can, in many cases, be absolutely devastating. The once prevalent notion that achieving ICU survival was a sufficient goal has now been shown to be naïve. No doubt, the focus of ARDS clinical research over the next 10 yr will move substantially in the direction of securing more high-quality outcomes.

NONPHARMACOLOGIC INTERVENTIONS

By the end of the 1990s the benefits from the general improvements in critical care were reaching a plateau, and it was becoming clear that intensive study of well-accepted but unproven usual care was in order so as to confirm that what seemed reasonable was truly useful and not harmful in producing optimal outcomes (72).

Extracorporeal Membrane Oxygenation

Nonpharmacologic therapeutic interventions have been studied in ARDS, and as with pharmacotherapy, few have met with success. One of the first nonpharmacologic randomized trials in

Figure 1. Survival rates for ARDS have been increasing steadily as indicated from the reports of *Milberg, 1995 (51); †Weidemann – surfactant (56); ‡ARDSNet – low tidal volume (55); and **ARDSNet – low PEEP (62).

ARDS evaluated extracorporeal membrane oxygenation in the late 1970s based on the concept that extracorporeal support of respiration could be accomplished safely and allow the lungs to “rest” and heal (13). Enticing as that idea was, this trial and later investigations were unable to prove that outcomes were improved using this technique (73).

Prone Positioning

Prone positioning to improve oxygenation in patients with ARDS was proposed more than 20 yr ago. Formal trials have been conducted to evaluate whether prone positioning can improve survival and to identify which categories of patients can benefit from prone positioning. To date, its use is inconclusive and more study will be required to establish the optimal ventilatory setting to be selected before, during, and after positioning; to determine the duration and frequency of positioning; and to standardize the maneuver (74).

Tidal Volume

Over the decades of the '70s, '80s, and '90s a plethora of investigations explored various means of improving oxygenation with a variety of ventilator approaches. An observational study by Hickling and coworkers (75), along with data from animal studies, raised interest in lower tidal volume ventilation. Critical care textbooks had long recommended tidal volumes of 10 to 15 ml/kg actual body weight (76). These tidal volume recommendations seemed quite useful and safe in postoperative abdominal surgery patients with normal lungs, the first major patient group to receive long-term ventilator support back in the 1960s when postoperative recovery rooms were evolving into long-term intensive care units. For the first 10 to 15 yr after recognition of ARDS there was little question whether those same tidal volumes were also appropriate for patients with injured lungs.

As it became clear that patients with ARDS had much smaller lung volumes than their normal postoperative counterparts, the

Figure 2. Several measures of long-term disability in surviving ARDS patients indicate slow and incomplete recovery. Data from Herridge, 2003 (67). Solid bars: forced vital capacity (% predicted); striped bars: 6-minute walk (% predicted); open bars: return to work (%).

Figure 3. Venn diagram showing relative numbers of patients with acute respiratory failure (intubation and mechanical ventilation > 24 h), acute lung failure (ARF patients with $\text{PaO}_2/\text{FiO}_2 > 300$ mm Hg not explained by ventilatory failure), acute lung injury, and ARDS. Note that although ARDS makes up most of the population of ALI, ALI is a small fraction of the population with acute respiratory failure (see text definition). The total number of patients who would meet ALF criteria (i.e., abnormal oxygenation and bilateral infiltrates) is not known, but is substantially greater than the ALI population. (Adapted from Luhr and colleagues [124]).

thought of reducing tidal volumes as proposed by Hickling gained favor (75–77). In the 1990s, several small randomized trials were conducted using smaller versus larger tidal volumes (78–81). Although all of these had severe limitations with regard to the statistical power needed to detect a difference, one of these (81) was able to show a survival benefit from the use of smaller tidal volumes (6 ml/kg actual body weight) in conjunction with other strategies designed to protect the lung such as lung recruitment maneuvers. In 1986, CT scanning was used to dispel the common belief that the ARDS lung was “stiff” only because of low compliance of the respiratory system. Instead, it was found that decreases in respiratory compliance were closely associated with the greatly reduced amount of normally aerated tissue (baby lung), which received most of the insufflated gas. Those observations led to further studies of lung protective strategies (32, 34, 35, 82–85). Other potential mechanisms include the hypothesis that hypercapnic acidosis attenuates acute lung injury (84).

When the NIH National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network (ARDSNet) was launched in 1994, there were a number of interesting pharmacologic interventions considered for the inaugural study to be conducted by this group. However, it rapidly became apparent that even the most basic nonpharmacologic ARDS intervention, mechanical ventilation, had received almost no attention in large randomized clinical trials.

The ARDSNet designed a prospective randomized trial to determine if 6 ml/kg predicted (not actual) body weight and plateau airway pressure limitation to 30 cm/H₂O would provide better outcomes in patients with ALI than 12 ml/kg predicted body weight (PBW). The latter, PBW, translates, on average, to between 10 and 11 ml/kg *actual* body weight due to the fact that in this study, the average patient with ARDS weighed about

20% more than their PBW. (55). Six milliliters/kilograms PBW is nearly the same as normal tidal volume in spontaneously breathing volunteers (85). Changes in body weight due to fluid volume accumulation and increased adipose tissue, of course, do not change lung size. Hence any tidal volume formula that uses actual body weight is subject to error in a given patient. The ARDSNet trial, planned for enrollment of 1,000 subjects, stopped early because of a striking reduction in hospital mortality in the 6 ml/kg PBW group (31% versus 39.8%, $p = 0.007$). The lower tidal volume group also experienced lower levels of circulating inflammatory markers such as IL-6, less time requiring mechanical ventilation, and less nonpulmonary organ failure (55). It is imperative that the search for even safer forms of mechanical ventilation, the principal life support for patients with ALI, continue because the mortality rate is still too high. At least now there is an explicit methodology that produces an excellent survival to which other methods, new or old, can be compared.

Positive End-Expiratory Pressure

Animal models and early observations (86–89) readily and convincingly established that maintaining positive pressure throughout the respiratory cycle could greatly improve oxygenation in patients with ARDS. This effect was presumed to be due to the prevention of collapse of surfactant deficient small airways and alveoli during expiration. The lack of adequate functional surfactant made reinflation very difficult, requiring high airway pressures. Thus in established ALI, positive end-expiratory pressure (PEEP) has been adopted for routine management to recruit, reduce oxygen requirements, and improve compliance. Further, by keeping alveoli open throughout the respiratory cycle, damage produced by the repetitive opening and closing may be prevented (79, 90). The range of PEEP used in practice is wide and has even included use of very high levels of PEEP (91, 92). Thus, though PEEP is widely accepted as useful and is used nearly universally to support patients with ALI, the doses needed to accomplish maximum benefit to survival with minimum complications have never been established in humans and are even very limited in animals.

The ARDSNet designed a trial of lower versus higher PEEP levels in attempt to begin to assess the relative benefits of two different PEEP levels (62). PEEP level separation at various FiO_2 levels was in the range of 6 cm H₂O (mean of 14 versus 8 cm H₂O) while otherwise providing the standardized 6 ml/kg PBW protocol standard of the ARDSNet. To also examine the effect of recruitment maneuvers (93–96), a subset of the patients with higher PEEP in this study were randomized to also receive a 30-s period of 35 to 40 cm H₂O continuous positive airways pressure (CPAP) versus a “sham” recruitment maneuver. These interventions produced only modest effects on oxygenation and were not durable, lasting less than one hour. Safety concerns having to do with transient declines in blood pressure also limited this approach, and they were dropped from the trial when enrollment was still less than 10% (97). The group with higher PEEP experienced clear increases in oxygenation efficiency as measured by $\text{PaO}_2/\text{FiO}_2$ and lung compliance was greater, but no benefit to survival, time on ventilator, or nonpulmonary organ function was able to be shown. Furthermore, no benefit of higher PEEP was observed among patients with direct versus indirect injury, nor by severity of initial gas exchange abnormality (62). The authors of this study acknowledge that it does not exclude the possibility of benefit from other PEEP or recruitment maneuver strategies, and they encouraged future studies.

Importantly, however, the study of higher versus lower PEEP confirmed that when ventilated with 6 ml/kg PBW both groups had 28-d mortality rates near 25%, as was observed in the earlier ARDSNet lower tidal volume study (55). These results also

suggest that within the range of values tested, higher levels of PEEP are either not harmful or there are off-setting risks and benefits. Given these findings, use of the original ARDS Network 6 ml/kg PBW tidal volume strategy and PEEP- FiO_2 scale as a starting point for ventilation is recommended but routine use of recruitment maneuvers is not. However, it would be reasonable to reserve higher levels of PEEP and/or recruitment maneuvers for patients with refractory hypoxemia in an attempt to improve oxygenation when severity of the oxygenation defect is the most immediate threat to survival.

Fluid Management for Increased Permeability Pulmonary Edema

Under conditions of microvascular injury, lung water accumulates to a greater degree compared with normal lung at the same microvascular pressures (98, 99). Short-term (i.e., < 24 h) animal experiments indicate that reducing lung water improves oxygenation and lung compliance (99). Human trials demonstrate improved physiologic endpoints with a variety of approaches to reduce lung water including diuresis without vascular pressure measurement, intravascular pressure targeted diuresis, and diuresis guided by sophisticated measures of lung water (99, 100). On the other hand, many patients with ALI are unstable hemodynamically, and there are abundant data to suggest that prompt resuscitation of such patients improves outcome (101), whereas the same resuscitative efforts administered later may not be helpful and are perhaps harmful (99, 100, 102). There remains controversy regarding the role of invasive monitoring to guide fluid resuscitation (103). In spite of extensive animal and human research, this perennial question remains unanswered in ARDS management. The NHLBI ARDSNet is undertaking the largest trial to date in attempt to answer the question of whether conservative or liberal fluid management provides better long-term outcome in ALI.

PHARMACOLOGIC INTERVENTIONS

There have been only a handful of pharmacologic therapies tried in ARDS, and those had only limited success and require further study (surfactant, inhaled nitric oxide, partial liquid ventilation, and corticosteroids) (104–109). There is probably no greater controversy in the treatment of ALI than whether or not to use steroids, and if so, when and at which dose. As far back as the landmark study by Ashbaugh and coworkers in 1967, the value of steroids was thought to be in their antiinflammatory and antiedema effect (11). Numerous trials of corticosteroids in humans at risk for ARDS have failed to demonstrate benefit (105–109). Likewise, despite the exuberant inflammatory reaction in the alveoli, rigorous human clinical studies indicate that high dose glucocorticoids do not modify the course of ARDS when given early in the course of the process (109).

Despite failed studies of prevention or early treatment, a great deal of interest remains in the use of corticosteroids for the “salvage” of patients with persistent ARDS. Although this practice has often been termed treatment of the fibroproliferative phase, biopsy and histologic documentation of fibroproliferation is not usual. Several small case series suggest some clinical benefits of extended therapy with moderate to high dose glucocorticoids (110–112), including modification of the inflammatory response. Eventually a small, prospective randomized cross-over design controlled trial was conducted. Eight patients with ARDS persisting more than 7 days were randomized to placebo and 16 to high-dose methylprednisolone therapy (113). Half of the patients randomized to placebo were crossed over to treatment because of failure to improve their lung injury score by one point or more, whereas no patient treated with corticosteroids

crossed over. When patients were analyzed “as randomized” a significant reduction in mortality was observed; if analyzed “as treated” there was no survival benefit (114).

The ARDSNet has recently completed a large randomized, blinded trial of methylprednisolone versus placebo. Preliminary results presented indicate no difference in 28- or 60-d mortality, despite improvements in gas exchange, blood pressure, and time on ventilator among patients given methylprednisolone (59). Conclusions about the value of corticosteroids in persistent ALI must await final results of this study and almost certainly will be controversial. Given the lack of conclusive evidence for improvement in mortality, support for routine use of steroids for persistent ALI remains elusive. Further, data implicating steroids in the long-term disability of patients with ALI raises safety concerns (67).

Early investigators hypothesized that surfactant deficiency was an important component in ARDS, as it is in infant respiratory distress syndrome. Several small studies of surfactant therapy suggest that administration to patients with ALI may improve oxygenation, but future trials must determine the optimal dosage and delivery system, timing, and actual preparation, as well as effects on long-term outcome. At this time surfactant therapy is not recommended for adult ALI (58).

Anticoagulant therapy may be useful in the treatment of ALI. A variety of coagulation inhibitors have been tested including heparin, antithrombin, tissue factor pathway inhibitor, factor VIIa, activated protein C, and thrombomodulin in animal models and/or humans with either sepsis or ALI (115). To date only activated protein has been proven useful in severe sepsis, though it is not clear that it directly improves lung function (116).

FUTURE DIRECTIONS

Much more work is needed to define the basic mechanisms that (1) initiate lung injury before institution of positive pressure ventilation, (2) mediate progression of ongoing lung injury, (3) cause persistent fibrosis and pulmonary hypertension, and (4) mediate the propagation of injury from the lung to other organs in many patients with ALI. In 2002 the NHLBI convened a working group to consider future directions in ARDS research, and the conclusions were that there are major unanswered questions that will require continued major multidiscipline research efforts. This will require sophisticated databases and bioinformatic tools that can handle large volumes of complex data as the genomics and proteomics of ALI are explored. Modern analytic techniques are needed, including microarray interrogation, proteomic analysis, laser capture microdissection, and more. Advanced imaging such as microcomputerized tomography and confocal microscopy should be refined to generate data on cell and parenchymal microstrains in intact lungs, so that molecular research on mechanosensing and mechanotransduction can be interpreted in an appropriate context. Imaging inflammatory cell trafficking and cell–cell interaction will likely be informative. Genetically altered mouse models, lung- and tissue-specific conditional knockouts, and overexpression of candidate genes will be needed (117, 118).

Future directions in clinical investigations designed to validate current ARDS therapy or test new treatments will be challenging from an ethical perspective, both because the subject is usually unconscious or otherwise unable to consent for themselves, and because entrenched, but unproven treatments, abound (118–120). The ARDSNet tidal volume trial (54) and the FACTT trial (ongoing) were criticized for the selection of control arms and for variations in informed consent documents (121–123). Although the protection of human research subjects should be the highest priority in critical care research, what must be dealt with in a straightforward systematic manner is the recognition that so many of the interventions used to support

patients with ARDS have never been subjected to formal testing using modern clinical trial standards and may prove beneficial or harmful when studied.

In the past few years, new information has emerged about a group of patients who spend a substantial amount of time dependent on mechanical ventilation due to acute processes that are poorly defined. This population includes patients requiring more than 24 hours of mechanical ventilation. This group may make up one of the largest groups of mechanically ventilated patients in healthcare and have been referred to by Luhr and colleagues as acute respiratory failure (ARF) (124). Much more research is needed in order to more fully characterize this very large group.

SUMMARY

The past 100 years (especially the last 50 years) of ARDS research and advances in the clinical care of patients with ARDS is a fascinating picture that spans the timeframe of so many other major medical and scientific advances. Tools such as the highly instrumented animal model, cell biology, molecular biology, advances in imaging from the micro to macroscopic, and genetics have greatly facilitated our understanding of this complex syndrome. The scientific foundation is strong and will provide a firm basis upon which the next chapter in this saga can be written. With only a little imagination, a day can be seen when the mortality and the long-term morbidity of ARDS will be reduced to only that of the preexisting underlying diseases, if any.

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