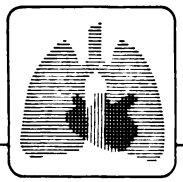

clinical investigations in critical care

Improved Survival in ARDS Patients Associated with a Reduction in Pulmonary Capillary Wedge Pressure*

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The survival and ICU length of stay of 40 ARDS patients admitted to the ICU were analyzed to determine if a management strategy of lowering the pulmonary capillary wedge pressure (Ppw) was associated with an increased survival or a decreased ICU length of stay. ARDS was defined as three or four quadrant alveolar filling roentgenographically, a PaO_2 <80 mm Hg with an FIo_2 >.5 and a Ppw <18 mm Hg. Patients were divided into two groups: group 1 included all patients in whom there was a reduction of Ppw by at least 25 percent, and group 2 included patients in whom there was no, or less than a 25 percent reduction in Ppw. Survival was statistically different between the groups with 12 of 16 group 1 patients and seven of 24 group 2 patients surviving to hospital discharge. This difference remained statistically significant after stratifying patients by age and the APACHE II severity of illness index. We conclude that this retrospective analysis supports the notion that treatment of low pressure pulmonary edema with reduction of Ppw is associated with an increased survival.

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EVLW = extravascular lung water

The adult respiratory distress syndrome is a pathophysiologic condition initiated by direct pulmonary or systemic insults and characterized by a pulmonary capillary leak resulting in alveolar flooding. This lung flooding causes severe hypoxemia secondary to intrapulmonary shunt, lung stiffness, and diffuse alveolar infiltrates on chest x-ray film.[1] Supportive therapies for patients developing this acute lung lesion include early and elective intubation, high fractions of inspired oxygen (FIo_2) to prevent life-threatening hypoxemia, and titration of positive end expiratory pressure to reduce intrapulmonary shunt and allow reduction of FIo_2 to a nontoxic level.[1-3] Despite this aggressive supportive therapy, mortality in this syndrome has remained high and perhaps unchanged since the advent of these innovations.[4-6]

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Conceivably, reduction of hydrostatic pressures in the pulmonary circulation, as judged by the measured Ppw, could reduce the pressure gradient driving edemagenesis and promote clearing of lung water, and thus, shorten the duration of potentially dangerous supportive therapy. Such a strategy has been investigated in canine models of acute lung injury with convincing evidence that reduction of intravascular volume as judged by the Ppw does reduce lung edema and improve gas exchange.[7-9] Approaches incorporating this notion have been recommended by some clinicians in the fluid management of patients with ARDS,[1,9] and in our own institution, many patients are managed in accord with the principle of seeking the lowest Ppw consistent with an adequate cardiac output. Accordingly, we sought information to illuminate this issue by retrospectively analyzing the hemodynamic management, the ICU length of stay, and survival of all patients admitted to our intensive care unit with ARDS over a 36-month interval. Patients were divided into two groups according to whether or not a Ppw reduction of at least 25 percent was achieved during their acute management. The patient groups were then analyzed in terms of demographic and clinical data, severity of illness, and outcome, including length of ICU stay and survival.

Materials and Methods

We performed a retrospective analysis of our experience caring for patients with ARDS who were admitted to our intensive care unit over a three-year period from January 1984 to January 1987.

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The list of patients was generated from our ICU data base which tracks all admissions and major diagnoses including all patients with a diagnostic listing of ARDS. Patient charts were reviewed by the principal investigators to determine eligibility for inclusion in the study.

Patients with the following ARDS criteria were studied:

1. At least three quadrant infiltrates present on chest roentgenogram;
2. $PaO_2 \leq 80$ mm Hg with $FIo_2 > 0.5$ and;
3. Ppw ≤ 18 mm Hg.

The third criterion limited patient enrollment to those individuals undergoing pulmonary artery catheterization. Data collection from chart review included demographic data (age, sex, dates of hospitalization, dates in the ICU, major diagnosis and survival); physiologic data (arterial blood gas analysis, chest roentgenogram interpretation, hemodynamic and ventilation data, use of vasoactive agents, methods employed to reduce the Ppw and complications); and APACHE II data (12 physiologic measurements and chronic health status indicators). The APACHE II data were used to prognostically stratify these acutely ill patients.

The physiologic parameters were collected at entry, 24 hours and 48 hours. After the data were collected, patients were divided into two groups. Group 1 included patients in whom there was a reduction of Ppw by at least 25 percent. Group 2 patients were those in whom there was no reduction of Ppw or a reduction less than 25 percent. The ICU length of stay of the two groups was compared using the Student's *t*-test. The survival of the two groups after stratifying for age and APACHE II was compared using the Mantel-Haenzel statistic.[10] The levels of PEEP, FIo_2, and cardiac output in survivors and nonsurvivors were compared using repeated measures analysis of variance. A p value of less than 0.05 was considered statistically significant.

Table 1—*ARDS Patient Characteristics (N = 40)**

		Group 1 (N = 16)		Group 2 (N = 24)	
		Mean	Range	Mean	Range
Age, yr		35	(16-78)	53	(21-81)
Prob die, % (by APACHE II)		15	(13-17)	14	(1315)
Mean Ppw					
Entry		13.0	(9.0-17.0)	11.4	(9.4-13.4)
24 hours		6.5	(2.0-11.0)	13.0	(8.0-18.0)
48 hours		7.7	(6.2-9.2)	13.0	(6.9-19.1)
Heart rate	at 0	126	(88-165)	111	(70-163)
Heart rate	at 24	124	(94-158)	109	(60-144)
Heart rate	at 48	111	(84-130)	107	(64-140)
MAP (mm Hg)	at 0	86	(64-127)	85	(57-138)
	at 24	83	(51-122)	80	(52-119)
	at 48	91	(77-114)	80	(42-110)
PEEP	at 0	9	(0-15)	6	(0-15)
	at 24	9	(0-15)	8	(0-20)
	at 48	10	(0-15)	10	(0-20)
FIo_2	at 0	0.86	(0.5-1.0)	0.72	(0.4-1.0)
	at 24	0.65	(0.3-1.0)	0.62	(0.4-1.0)
	at 48	0.60	(0.4-1.0)	0.55	(0.4-1.0)
Creatinine	at 0	1.9	(0.9-2.9)	1.8	(1.0-2.6)
	at 24	1.7	(0.8-2.7)	2.0	(0.9-2.9)
	at 48	1.9	(0.8-2.9)	1.8	(0.9-2.4)

*Data points for Ppw, heart rate, MAP (mean arterial pressure), PEEP, FIo_2, and creatinine are taken at 0 (entry), 24 hours, and 48 hours into therapy.

Results

Forty patients met previously mentioned ARDS criteria and included equal numbers of men and women (Table 1). The mean age of our patients was 46 with a range from 16 to 81. The mean Ppw for all patients at entry into the study was 12 mm Hg and subsequently was reduced to 10 mm Hg at 24 and 48 hours of therapy. The mean probability of death as predicted by APACHE II score on the day of meeting ARDS criteria was 17 percent.

The mean length of stay in the ICU was 12 days, while the mean length of hospitalization was one month. As described earlier, patients were divided into two groups for comparison of response to Ppw reduction. Group 1 patients were those in whom there was at least a 25 percent reduction in Ppw and group 2 patients were those in whom this reduction was not achieved. Ultimately, there were 16 patients in group 1 and 24 patients in group 2. Methods used to lower the Ppw included diuretic administration, fluid restriction, phlebotomy, dialysis, and ultrafiltration.

All patients in both groups were treated with furosemide. Five of 16 patients in group 1 and 14 of 24 patients in group 2 were treated with a second diuretic (metolazone, ethacrynic acid, or spironalactone) in addition to furosemide. No patient received more than two diuretics.

Two patients in group 1 and three patients in group 2 were treated with phlebotomy of between 150 ml and 350 ml of blood.

Three patients in group 1 and seven patients in group 2 underwent at least two sessions of dialysis or ultrafiltration.

The mean Ppw for patients in group 1 at entry was 13 mm Hg (Table 1), and although not statistically significant, was higher than the mean Ppw at entry in group 2 patients where it was 11.4 mm Hg. By 24 and 48 hours into therapy, the mean Ppw had decreased to 6.5 mm Hg and 7.7 mm Hg, respectively in Group 1 patients, but had actually increased to 13.0 mm Hg in group 2 patients.

When comparing differences in outcome and survival between groups 1 and 2, there was a statistically significant difference with 75 percent of patients in group 1 surviving compared with 29 percent of patients in group 2 (Table 2). This difference remained statistically significant after stratifying patients by age and

Table 2—*Survival and ICU Length of Stay*

	Group 1 (N = 16)	Group 2 (N = 24)
Survived	12 (75%)	7 (29%)*
ICU length of stay (days)	8.9 ± 8	14.8 ± 11.4 days

*$p < 0.02$ chi square, Mantel-Haenzel.

by APACHE II scores. Although ICU length of stay was shorter for patients in group 1 with a mean stay of 8.9 days compared with group 2 with a mean stay of 14.8 days, this difference was not statistically significant (Table 2).

The PEEP and FIO_2 requirements did not differ significantly between groups 1 and 2 at entry. Survivors in both groups 1 and 2 had lower PEEP and FIO_2 levels over the 48-hour period of data collection.

Discussion

The acute lung injury in ARDS leads to alveolar flooding with proteinaceous fluid producing lung mechanical and gas exchange abnormalities.[1] Pathologically, this early or exudative phase spanning the first one to five days following lung injury is characterized by alveolar flooding, inflammatory cell infiltrate, and hyaline membrane formation, with minimal destruction of lung architecture.[11] This can well be thought of as a reversible lung lesion, since patients recovering at this point in their illness go on to recover normal lung function.[12] Within one to two weeks, patients still requiring mechanical ventilatory support often manifest extensive pulmonary fibrosis and distortion of lung architecture, entering a pathologic condition termed the proliferative phase of acute alveolar damage.[11]

Interventions aimed at the cellular mechanisms of lung injury and its perpetuation could benefit such patients. Since data available both from animal models of acute lung injury and from patients with this syndrome implicate complement and leukocyte activation in many forms of pulmonary capillary leak, interest is keen to identify and test interventions to minimize injury and improve outcome.[13-16] Nonetheless, no such therapies are currently available for clinical application. Indeed, a recent prospective clinical study evaluating the efficacy of steroid therapy in patients at risk for the development of ARDS, and hence, treated very early in their course, demonstrated no benefit with this intervention.[17]

Thus, state-of-the-art therapy for this disorder is centered upon supportive measures while the precipitating causes of ARDS—such as sepsis, pulmonary infection, aspiration, or pancreatitis—are treated. While supportive therapy with mechanical ventilation and PEEP are effective at achieving reduction of lung shunt, and thus improving gas exchange, it is clear that it does not reduce lung water but rather redistributes edema from the alveolar spaces to the peribronchial interstitium.[18] Indeed, as a clinical correlate to this physiologic effect of our therapy, patients tend not to succumb to hypoxia in the early course of the disease, but rather evolve either multiorgan failure most commonly due to the late emergence of sepsis or progression of their lung lesion to a late and irreversible fibrotic stage.[19-21]

In view of these aspects of ARDS and its treatment, interventions that reduce lung edema in the acute exudative phase of the disease process and thus shorten the duration and intensity of supportive therapies may improve outcome. In capillary leak induced in canine models by either intravenous oleic acid or endobronchial aspiration of HCL, reduction of Ppw by phlebotomy or sodium nitroprusside infusion reduces lung water and intrapulmonary shunt, thus resulting in improved gas exchange.[7-9,22-24] Extrapolation of these data from animal models of acute lung injury to the clinical situation is confounded by the fact that reduction of ventricular preload could potentially reduce cardiac output, and thus, cause unacceptable reduction of oxygen delivery to peripheral tissues. This is particularly pertinent in patients with sepsis and ARDS who exhibit a dependence of oxygen utilization over a wide range of oxygen delivery, a phenomenon termed pathologic supply dependency of oxygen utilization and thought to occur as a result of factors impairing oxygen extraction at a tissue level.[24-27] Thus, like all therapies directed at these critically ill patients, demonstrated benefit must be measured against potential complication or deleterious effect. Yet in both canine models of pulmonary vascular leak, cardiac output, oxygen delivery, and oxygen consumption were maintained when Ppw and edema were reduced by the clinically relevant therapies of plasmapheresis[8,22-24] and/or vasoactive drugs[7,22,23]

Available data from clinical studies do not adequately clarify the utility of this approach. Brigham and colleagues[28] reported that the amount of extravascular lung water measured by single-pass multiple tracer technique did not correlate with the magnitude of oxygenation defect or survival in patients with ARDS. This observation did not address, however, the question of whether interventions to reduce lung water in a given patient could be successfully carried out with improvement in lung function and outcome. Eisenberg et al[29] have reported that mortality was improved in patients with initially high EVLW and normal Ppw (predominantly patients with sepsis or ARDS) when EVLW was reduced with protocol management that included fluid restriction and diuresis. Finally, Simmons et al[30] have reported in a prospective data collection of patients with ARDS that survival was improved in those individuals with net fluid loss as gauged by input and output determinations as well as by weight change over the period of observation.

Our observations add to the available information regarding this approach to treatment. While retrospectively collected, our data clearly indicate that survival is improved in those patients who experience a 25 percent or greater reduction in Ppw as compared

to those who did not. The significant difference in survival is present when the patient groups were stratified by age or by severity of illness as determined by APACHE II score. While there was also a trend toward a reduced ICU stay in patients in whom there was a successful reduction in Ppw, this trend did not reach statistical significance. To the extent that future randomized clinical trials confirm this promising result, we speculate that one explanation is the shorter stay on the ventilator and in the ICU associated with reduced edema. Such an explanation does not conflict with the notion that the severity and duration of the pulmonary vascular leak is paramount in the mortality of patients with ARDS; rather, it acknowledges that whatever the cause and severity of the leak, the edema arising can be reduced so reducing the duration of critical care and the attendant complications, some of which are known to aggravate the vascular injury (sepsis, aspiration).

Since patients were not randomly and prospectively assigned to receive therapies aimed at reduction of Ppw, it is possible that our observation is an artifact of our treatment group harboring greater cardiac reserve, and thus, both tolerating this intervention but demonstrating improved survival despite its institution. Alternatively, the patient groups might differ substantially in ways which are difficult to evaluate and may be grouped under the term, "severity of illness." To the former objection, we would stress that the groups did not differ significantly in initial hemodynamics as judged by the Ppw or cardiac output. Indeed, the patients with the highest mean cardiac output were those in group 1 who did not survive. This finding is similar to that reported by Parker and colleagues,[31] who found a higher cardiac index in patients who did not survive septic shock than in nonsurvivors. Since sepsis was a frequent precipitant to ARDS in our patient population, a similar phenomenon may have been present. As to the second possibility of differences in severity of illness, our stratification of patients by APACHE II scoring failed to elicit differences in projected outcome. This method of comparison of diverse groups of critically ill patients has been shown to correlate well with survival for a wide variety of diagnostic categories.[32]

Since this investigation was not conducted prospectively, there was no possibility of predetermining the various interventions used by clinicians in this study to lower Ppw, and the modalities employed at our institution include fluid restriction, diuresis, phlebotomy, plasmapheresis, and ultrafiltration. We are unable to address the question of which intervention(s) are most beneficial in these patients, nor which of the several vasoactive drug regimens employed in our patients was most effective.

We conclude that reduction of Ppw in patients with ARDS can be safely achieved and has a beneficial effect on outcome in survival and possibly duration of ICU management. We feel further investigations of this intervention in patients should proceed with prospective and randomized clinical trials to confirm the ultimate impact on outcome.

References

1 Hall JB, Wood LDH. Acute hypoxemic respiratory failure. Medi Grand Rounds 1984; 3:183-95

2 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967; 2:319-23

3 Robin ED, Carey LC, Grenvik A, Glauser F, Gaudio R. Capillary leak syndrome with pulmonary edema. Arch Intern Med 1972; 130:66-71

4 Petty TL. Adult respiratory distress syndrome: Definition and historical perspective. Clin Chest Med 1982; 3:3-7

5 Rinaldo JE, Rogers RM. Adult respiratory distress syndrome: Changing concepts of lung injury and repair. N Engl J Med 1982; 306:900-08

6 Staub NC. Pulmonary edema due to increased microvascular permeability. Ann Rev Med 1981; 32:291-312

7 Prewitt RM, McCarthy J, Wood LDH. Treatment of acute low pressure pulmonary edema in dogs: Relative effects of hydrostatic and oncotic pressure, nitroprusside, and PEEP. J Clin Invest 1981; 67:409-18

8 Sznajder JI, Zucker A, Wood LDH, Long GR. The effects of plasmapheresis and hemofiltration on canine acid aspiration pulmonary edema. Am Rev Respir Dis 1986; 34:222-28

9 Wood LDH, Prewitt RM. Cardiovascular management in acute hypoxemic respiratory failure. Am J Cardiol 1981; 47:963-72

10 Mantel N, Hanszel W. Statistical aspects of the Analysis of Data from Retrospective Studies of Disease. Nat Canc Inst 1959; 22:719-48

11 Katzenstein AA, CM Bloor, AA Liebow. Diffuse alveolar damage—the role of oxygen, shock and related factors. Am J Pathol 1976; 85:211-24

12 Klein JJ, Van Haeringen JR, Sluiter HJ, Holloway R, Peset R. Pulmonary function after recovery from the adult respiratory distress syndrome. Chest 1976; 69:350-55

13 Skubitz KM, Craddock PR, Hammerschmidt DE, August JT. Corticosteroids block binding of chemotactic peptide to its receptor on granulocytes and cause disaggregation of granulocyte aggregates in vitro. J Clin Invest 1981; 68:13-20

14 Weinberg PF, Matthay MA, Webster RO, Roskos KV, Goldstein IM, Murray JF. Biologically active products of complement and acute lung injury in patients with the sepsis syndrome. Am Rev Respir Dis 1984; 130:791-96

15 Till GO, Johnson KJ, Kunkel R, War PA. Intravascular activation of complement and acute lung injury. Dependency on neutrophils and toxic oxygen metabolites. J Clin Invest 1982; 69:1126-35

16 Said SI, Foda HD. Pharmacologic manipulation of acute lung injury. Am Rev Respir Dis 1989; 139:1553-64

17 Luce JM, Montgomery B, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 1988; 138:62-8

18 Malo J, Ali J, Wood LDH. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? J Appl Physiol 1984; 57:1002-10

19 Hyers TM, Fowler AA. Adult respiratory distress syndrome: causes, morbidity, and mortality. Federation Proc 1986; 45:25-9

20 Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132:485-89

21 Bell RC, Coalson JJ, Smith JD, Johanson WG. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983; 99:293-98
22 Gottlieb S, Wood LDH, Hansen DE, Long GR. The effect of nitroprusside on pulmonary edema, oxygen exchange and blood flow in hydrochloric acid aspiration. Anesthesiology 1987; 67: 203-10
23 Long R, Breen PH, Mayers I, Wood LDH. Treatment of canine aspiration pneumonitis: fluid volume reduction vs. fluid volume expansion. J Appl Physiol 1988; 65;1736-44
24 Zucker A, Sznajder J, Becker CJ, Berger S, and Wood LDH. The pathophysiology and treatment of canine kerosene pulmonary injury: Effects of plasmapheresis and positive end-expiratory pressure. J Crit Care 1989; 4:184-93
25 Danek SJ, Lynch JP, Weg JG, Dantzker DR. The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. Am Rev Respir Dis 1980; 122:387-95
26 Kariman K, Burns SR. Regulation of tissue oxygen extraction is disturbed in adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132:109-14
27 Schumacker PT, Cain SM. The concept of a critical oxygen delivery. Intensive Care Med 1987; 13:223-29
28 Brigham KL, Kariman K, Harris TR, Snapper JR, Bernard GR, Young SL. Correlation of oxygenation with vascular permeability-surface area but not with lung water in humans with acute respiratory failure and pulmonary edema. J Clin Invest 1983; 72:339-49
29 Eisenberg PR, Hansrough JR, Anderson D, Schuster DP. A Prospective study of lung water measurements during patient management in an intensive care unit. Am Rev Respir Dis 1987; 136:662-68
30 Simmons RS, Berdine GG, Seidenfeld JJ, Prihoda TJ, Harris GD, Smith JD, et al. Fluid balance and the adult respiratory distress syndrome. Am Rev Respir Dis 1987; 135:924-29
31 Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984; 100:483-90
32 Knaus WA, Drapter EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13:818-29